Flovent Medicaid Dossier

This information is provided in response to your request for information about *Flovent*® Products (fluticasone propionate).

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In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

Table of Contents

1. Change Summary 4
2. Executive Summary. 5
3. Disease Description. 8
4. Product Description 9
4.1 Generic Name, Brand Name and Therapeutic Class 10
4.2 Dosage Forms and Package Sizes 10
4.3 AHFS or Other Drug Classification 11
4.4 FDA Approved and Other Studied Indications 11
4.5 Use in Special Populations 11
4.6 Pharmacology 11
4.7 Pharmacokinetics/Pharmacodynamics 12
4.8 Contraindications 12
4.9 Warnings/Precautions 12
4.10 Adverse Events 12
4.11 Other Clinical Considerations 12
4.12 Drug/Food/Disease Interactions 12
4.13 Dosing and Administration 12
4.14 Co-prescribed/Concomitant Therapies 15
5. Pivotal Efficacy and Safety Trials 15
5.1 Pivotal Efficacy and Safety Trails with Flovent Diskus in Children 4-11 with Asthma 15
5.2 Pivotal Efficacy and Safety Trials with Flovent Diskus in Adults and Adolescents with Asthma 18
5.3 Pivotal Efficacy and Safety Trials with Flovent HFA in Adults and Adolescents with Asthma 20
5.4 Pivotal Efficacy and Safety Trials with Flovent HFA in Children 4-11 with Asthma 24
6. Additional Safety Information 26
6.1 Studies Assessing the Effect on Hypothalamic-Pituitary-Adrenal Axis in Adults and Adolescents 26
6.2 Studies Assessing the Effect on Hypothalamic-Pituitary-Adrenal Axis in Children 30
6.3 Studies Assessing the Effects on Growth in Children 33
6.4 Studies Assessing the Effects on Bone Metabolism and Mineral Density in Children with Asthma 35
6.5 Studies Assessing the Effects on Bone Metabolism/Osteoporosis in Adults with Asthma 37
7. Comparative Data 41
7.1 Comparison with Montelukast in Children with Asthma 41
7.2 Comparison with Montelukast in Patients 12 Years of Age and Older with Asthma 44
7.3 Comparison with Beclomethasone Dipropionate HFA in Asthma 46
7.4 Comparison with Mometasone Furoate in Asthma 48
8. Other Studied Uses. 51
8.1 Use of Flovent HFA in Children Less than 4 Years of Age with Asthma . . 51
9. Outcome and Economic Evaluation 53
10. References 58

1. Change Summary

The following indicates section(s) within the *Flovent* Dossier where new clinical data has been added within the last year.

Flovent Diskus 50 mcg was made available in the United States in June 2007. The following sections provide clinical data related to the efficacy and safety of *Flovent Diskus*:

- Section 5.1 Pivotal Efficacy and Safety Trails with *Flovent Diskus* in Children 4-11 with Asthma
- Section 5.2 Pivotal Efficacy and Safety Trials with *Flovent Diskus* in Adults and Adolescents with Asthma

Flovent HFA was introduced with a dose counter in March 2007. The following section provides information regarding the dose counter:

- 4.13 Dosing and Administration

NIH Asthma Treatment Guidelines were revised and issued in August 2007. The following section summaries these recommendations:

- Section 2.0 Disease Description

2. EXECUTIVE SUMMARY

DISEASE: CONSENSUS TREATMENT GUIDELINES FOR ASTHMA

- National asthma management guidelines recommend for all patients the use of low-dose inhaled corticosteroids (ICS) as the preferred therapy for mild persistent asthma. Additionally, the use of an ICS either alone or in combination with adjunctive therapy is recommended as a preferred therapy for all severities of persistent asthma.(1)

BENEFITS OF *FLOVENT HFA* IN ASTHMA

- *Flovent HFA* Inhalation Aerosol contains the potent corticosteroid fluticasone propionate that helps to reduce inflammation in the airways, one of the main components of asthma.(2)
- *Flovent HFA* is available as pressurized, metered dose aerosol units for oral inhalation that delivers per actuation either 44, 110 or 220 mcg ex-actuator of a microcrystalline suspension of fluticasone propionate in an hydrofluoroalkane (HFA) propellant. It contains no excipients, soya lecithin, or chlorofluorocarbon (CFC) propellants.
- *Flovent HFA* is fitted with a dose counter that keeps track of the number of inhalations remaining, helping the patient to know when it is time for a prescription refill.
- The fluticasone propionate in *Flovent HFA* has negligible oral bioavailability (<1%) due to incomplete absorption from the gastrointestinal tract and extensive first-pass metabolism by the liver.
- *Flovent HFA* had 30% and 55% lower systemic exposure in healthy adults and children with asthma, respectively, compared with *Flovent* CFC.
- *Flovent HFA* provided an onset of effect on Day 1 for all 3 strengths with significant improvement in FEV_1 noted at Week 1, the first spirometry analysis time-point, compared with placebo. Maximum benefit may not be achieved for 1 to 2 weeks or longer.
- *Flovent HFA* is approved for use in children 4 years of age and older with asthma.
- *Flovent HFA* is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.
- Adverse events in clinical trials with *Flovent HFA* were similar to placebo.

EFFICACY OF *FLOVENT HFA* IN ASTHMA

- Three 12 to 16-week US pivotal trials in 980 adolescent and adult patients (≥12 years old) with asthma evaluated the efficacy and safety of *Flovent HFA*.(2,3,4) Patients receiving *Flovent HFA* had greater improvements in lung function, asthma symptom scores, and use of rescue albuterol compared to the placebo group. In Study 3, *Flovent HFA* enabled more patients (59% and 56% in the groups treated with *Flovent HFA* 440 and 880 mcg, respectively, twice daily) to eliminate oral prednisone as compared to placebo (13%).
- Two long-term studies of 6 months and 1 year duration showed that efficacy was maintained throughout the duration of the studies in patients receiving *Flovent HFA* . None of the patients were withdrawn due to lack of efficacy. The pattern of adverse events was similar to that observed in the 12-week studies.(2)
- A 12-week clinical trial evaluated the safety and efficacy of *Flovent HFA* 88 mcg twice daily in 241 children 4 to 11 years of age.(5) *Flovent HFA* improved peak expiratory flow, reduced daily rescue albuterol use, and reduced nighttime awakenings compared to placebo. Additional safety and efficacy of *Flovent HFA* in children is supported by adequate and well-controlled studies in patients 12 years of age and older, pharmacokinetic studies in children 4 to 11 years old, and the established efficacy of other inhaled formulations of *Flovent* in children 4 to 11 years of age.(2)
- In 4 head-to-head comparative clinical trials in adolescent and adult patients, *Flovent HFA* was clinically equivalent to *Flovent* CFC at the same doses. (6,7) (8) (9)

SAFETY OF *FLOVENT HFA*

- Particular care is needed for patients who are transferred from systemic corticosteroids to *Flovent HFA* because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of inadequate adrenal response.(2)
- Co-administration of fluticasone propionate and ritonavir (a highly potent cytochrome P450 3A4 inhibitor) is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
- *Flovent HFA* is not a bronchodilator and is not indicated for rapid relief of bronchospasm.
- Patients treated with *Flovent HFA* should be observed carefully for any evidence of systemic corticosteroid effects. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when *Flovent HFA* is administered at higher than recommended doses over a prolonged period of time.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A 52-week, placebo-controlled US study assessed the potential growth effects of *Flovent* inhalation powder 50 and 100 mcg BID, via Diskhaler in 325 prepubescent children 4 to 11 years of age. A subset analysis of children who remained pre-pubertal during the study revealed growth rates of 6.10 (placebo; n = 57), 5.91 (50 mcg; n = 74), and 5.67 cm/year (100 mcg; n = 79). The clinical significance of these growth data is not certain. The growth of children and adolescents receiving orally inhaled corticosteroids, including *Flovent HFA*, should be monitored routinely (e.g., via stadiometry).
- Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including *Flovent*.
- In clinical studies with *Flovent*, the development of localized infections of the pharynx with Candida albicans has occurred.
- Adverse events with *Flovent HFA* were similar to placebo. The most common adverse events (>5%) reported in clinical trials with *Flovent HFA* 44, 110, and 220 mcg twice daily, respectively (and placebo) in patients ≥12 years of age were: upper respiratory tract infection – 18%, 16%, 16% (14%), throat irritation – 8%, 8%, 10% (5%), sinusitis/sinus infection – 6%, 7%, 4%, (3%), hoarseness/dysphonia – 2%, 3%, 6%, (<1%), cough – 4%, 6%, 4%, (5%), bronchitis – 2%, 2%, 6%, (5%), and headache – 11%, 7%, 5%, (6%).

INDICATIONS FOR *FLOVENT HFA*

- *Flovent HFA* is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time. *Flovent HFA* is not indicated for the relief of acute bronchospasm.(2)

DOSING FOR *FLOVENT HFA*

- The recommended dosages of *Flovent HFA* for patients ≥ 12 years were based on prior asthma therapy Table 1. The recommended pediatric dosage is 88 mcg twice daily regardless of prior therapy. After asthma stability has been achieved, it is always desirable to titrate to the lowest effective dosage to reduce the possibility of side effects.

Table 1. Recommended Dosages for *Flovent HFA*[2]

	Recommended Starting Dosage	Highest Recommended Dosage
Pediatric 4 to 11 years*	88 mcg twice daily	88 mcg twice daily
Patients ≥12 years		
Bronchodilators alone	88 mcg twice daily	440 mcg twice daily
Inhaled corticosteroids	88 - 220 mcg twice daily	440 mcg twice daily
Oral corticosteroids	440 mcg twice daily	880 mcg twice daily

BENEFITS OF *FLOVENT DISKUS* IN ASTHMA

- *Flovent Diskus* contains the potent corticosteroid fluticasone propionate which helps to reduce inflammation in the airways of patients with asthma.[10]
- *Flovent Diskus* 50 mcg is available in a *Diskus* device with 60 doses (1 month supply) and a build-in dose counter that keeps track of the number of inhalations remaining.
- *Flovent Diskus* is approved for use in patients 4 years of age and older with asthma.
- Inspiratory flow rates were sufficient to deliver an effective dose in children with asthma 4 and 8 years old using *Flovent Diskus*.
- The fluticasone propionate in *Flovent Diskus* has negligible oral bioavailability (<1%) due to incomplete absorption from the gastrointestinal tract and extensive first-pass metabolism by the liver.
- *Flovent Diskus* had significant improvement in FEV_1 noted at week 1, the first spirometry analysis time point, compared with placebo. Maximum benefit may not be achieved for 1 to 2 weeks or longer.
- Adverse events in clinical trials with *Flovent Diskus* were mostly mild to moderate in severity.

EFFICACY OF *FLOVENT DISKUS* IN ASTHMA

- Three 12-week, placebo-controlled pivotal studies in 941 children 4-11 years of age, half of whom were receiving inhaled corticosteroids at baseline, showed significant improvements in pulmonary function and were less likely to discontinue therapy due to asthma deterioration while receiving *Flovent Diskus* 50 mcg or 100 mcg twice daily compared with placebo.[10,11] [12]
- Four 12-week, placebo-controlled pivotal studies conducted in 1036 adolescent and adult patients with persistent asthma randomized to *Flovent Diskus* 100 mcg, 250 mcg, or 500 mcg twice daily showed that measures of pulmonary function were statistically significantly improved compared with those of the placebo arm.[13,14,15] In addition, patients on *Flovent* were significantly less likely to discontinue study participation due to predetermined criteria of asthma deterioration.

SAFETY OF *FLOVENT DISKUS*

- Particular care is needed for patients who are transferred from systemically active corticosteroids to *Flovent* because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of inadequate adrenal response.[10]
- Co-administration of fluticasone propionate and ritonavir (a highly potent cytochrome P450 3A4 inhibitor) is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
- *Flovent* is not a bronchodilator and is not indicated for rapid relief of bronchospasm.
- Patients treated with *Flovent* should be observed carefully for evidence of systemic corticosteroid effects. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal

suppression (including adrenal crisis) may appear in a small number of patients, particularly when *Flovent* is administered at higher than recommended doses over a prolonged period of time.

- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A one - year, placebo - controlled US study assessed the potential growth effects of *Flovent* (inhalation powder) via Diskhaler at 50 and 100 mcg BID, in 325 prepubescent children 4 to 11 years of age. A separate subset analysis of children who remained pre-pubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year (placebo; n = 57), 5.91 cm/year (50 mcg group; n = 74), and 5.67 cm/year (100 mcg group; n = 79). The clinical significance of these growth data is not certain. The growth of children and adolescents receiving orally inhaled corticosteroids, including *Flovent Diskus*, should be monitored routinely (e.g., via stadiometry).
- Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including fluticasone propionate.
- In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with Candida albicans has occurred.
- Adverse events with *Flovent Diskus* were mostly mild to moderate in severity, with <2% of patients discontinuing the studies because of adverse events. The most common adverse events (>5%) reported in clinical trials with *Flovent Diskus* 50 mcg twice daily and placebo, respectively, in patients ≥ 4 years old were: upper respiratory tract infection - 20% vs. 16%, throat irritation - 13% vs. 8%, sinusitis/sinus infection - 9% vs. 6%, nausea and vomiting- 8% vs. 4%, fever- 7% vs. 4%, and headache - 12% vs. 7%.

INDICATIONS OF *FLOVENT DISKUS*

- *Flovent Diskus* is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time. *Flovent Diskus* is not indicated for the relief of acute bronchospasm.[10]

DOSING FOR *FLOVENT DISKUS*

- The recommended starting dosages of *Flovent Diskus* for patients ≥ 12 years are 100 mcg to 1000 mcg twice daily based on prior asthma therapy. The highest recommended dosages are 500 mcg to 1000 mcg twice daily. For children 4-11 years, the recommended starting dosage is 50 mcg twice daily, and the highest recommended dosage is 100 mcg twice daily.[10]

3. DISEASE DESCRIPTION

ASTHMA: EPIDEMIOLOGY AND RISK FACTORS

Asthma is one of the most common chronic diseases in the United States. According to the American Lung Association's Trends in Asthma Morbidity and Mortality report, approximately 22.2 million Americans (6.5 million children) had asthma in 2005.[16] In addition, 12.2 million people, or 55% of the people who had asthma at the time of the survey, had experienced an asthma attack in the previous year. Health care use in 2005 included 488,594 asthma-related hospitalizations and approximately 1.8 million emergency department visits. Deaths from asthma in 2004 numbered 3,816.[17] The economic cost of asthma in 2005 was estimated at $19.7 billion.[16]

Atopy, the genetic susceptibility for the development of an IgE-mediated response to environmental allergens, is the strongest identifiable predisposing factor for developing asthma.[1]

ASTHMA: PATHOPHYSIOLOGY

Asthma is a chronic disease of bronchoconstriction, inflammation and remodeling of the airways.[1] In asthma, airway narrowing and subsequent airflow limitation lead to the symptoms of asthma. In an acute exacerbation, contraction of the bronchial smooth muscle, or bronchoconstriction, occurs in response to exposure to an inhaled allergen or irritant. The inflammatory reaction to an inhaled allergen involves a complex interaction of a variety of cells, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, smooth muscle cells, and epithelial cells. As inflammation becomes more progressive and the disease becomes more persistent, factors such as edema, inflammation, mucus hypersecretion, and hypertrophy and hyperplasia of the airway smooth muscle lead to further airflow obstruction. In addition, airway inflammation results in an increase in the existing airway hyperresponsiveness. Over time, permanent structural changes may occur which result in loss of lung function that may be only partially reversible with therapy, also known as airway remodeling. Some of the structural changes which may occur include thickening of the sub-basement membrane, subepithelial fibrosis, airway smooth muscle hypertrophy and hyperplasia, blood vessel proliferation and dilation, and mucous gland hyperplasia and secretion. The interaction between symptoms, airway obstruction, bronchial hyperresponsiveness, and inflammation determines the clinical manifestations and severity of asthma as well as the response to treatment.

ASTHMA: CLINICAL PRESENTATION

Patients with asthma have recurrent episodes of cough (particularly worse at night), wheezing, difficulty breathing, and chest tightness.[1] These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. Patients also experience bronchial hyperresponsiveness to various triggers. On physical examination, patients may exhibit hyperexpansion of the thorax (especially in children), use of accessory muscles, hunched shoulders, and chest deformity. Wheezing may occur during normal breathing or during a prolonged phase of forced exhalation, although wheezing may be absent between exacerbations. Patients may have increased nasal secretion, mucosal swelling and nasal polyps. In addition, atopic dermatitis/eczema or any other allergic skin condition may be present. Symptoms may be absent during the time of examination; therefore, a history of symptoms is important.

ASTHMA: NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM GUIDELINES

The 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma recommend to first assess severity in newly diagnosed patients to determine initial therapy for patients with asthma.[1] For patients who have been receiving long-term controller medications, the guidelines recommend regular assessments of asthma control for monitoring and adjusting therapy. The guidelines provide impairment and risk criteria to assess both asthma severity and asthma control for each of the three age ranges: 0-4 years of age, 5-11 years of age, and ≥12 years of age. Impairment is defined as the frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced. Risk is defined as the likelihood of either asthma exacerbations, progressive decline in lung function, or risk of adverse effects from a medication. In addition, the guidelines also recognize the use of validated assessment tools, like the Asthma Control Test and Childhood Asthma Control Test, to assess asthma control.

For each age range, there are six treatment steps which provide preferred, and for some steps alternative, treatment recommendations for both intermittent and persistent types of asthma. Inhaled corticosteroids, either alone or in combination with other controller medications, continue to be the preferred first-line therapy for children and adults with persistent asthma. The guidelines also recommend the use of a long-acting beta-agonist (LABA) and an inhaled corticosteroid (ICS) as a preferred therapy for patients ≥5 years of age whose asthma is uncontrolled on their current controller and for patients ≥12 years of age with moderate to severe persistent asthma who are new to controller therapy.

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

BRAND NAME: FLOVENT® HFA Inhalation Aerosol

GENERIC NAME: fluticasone propionate

THERAPEUTIC CLASS: Inhaled Corticosteroid (ICS), Anti-inflammatory

BRAND NAME: FLOVENT DISKUS® 50 mcg

GENERIC NAME: fluticasone propionate inhalation powder, 50 mcg

THERAPEUTIC CLASS: Inhaled Corticosteroid (ICS), Anti-inflammatory

4.2 Dosage Forms and Package Sizes

Table 2. *Flovent* HFA Product Description: Dosage Forms, Package Size, NDC and WAC

Dosage Strength	Description	Package Size	NDC #	WAC*
Flovent HFA 44mcg Inhalation Aerosol	10.6-g pressurized aluminum canister† containing 120 metered inhalations‡ delivering 44mcg per actuation	1 box	0173-0718-20	$78.77
Flovent HFA 110mcg Inhalation Aerosol	12-g pressurized aluminum canister† containing 120 metered inhalations‡ delivering 110mcg per actuation	1 box	0173-0719-20	$105.47
Flovent HFA 220mcg Inhalation Aerosol	12-g pressurized aluminum canister† containing 120 metered inhalations‡ delivering 220mcg per actuation	1 box	0173-0720-00	$163.82
*WAC = wholesale acquisition cost effective as of November 2007. WAC is the listed price to wholesalers and warehousing chains, not including prompt pays, stocking or distribution allowances, or other discounts, rebates or charge backs.				
†Each canister is supplied is fitted with a dose counter and supplied with a dark orange oral actuator with a peach strapcap. This actuator should be used only with *Flovent* HFA and not with any other product.				
‡The correct amount of medication in each inhalation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when the counter reads 000. Never immerse the canister into water to determine the amount remaining in the canister (“float test”).				

Flovent HFA Inhalation Aerosol: Delivers a microcrystalline suspension of fluticasone propionate in propellant HFA 134a. It contains no other excipients.

Table 3. *Flovent Diskus* Product Description: Dosage Strength, Package Size, NDC, and WAC

Dosage Strength	Description	Package Size	NDC #	WAC*
50 mcg	Disposable orange inhalation unit with integrated mouthpiece cover and dose counter within a plastic-coated, moisture-protective foil pouch.	60 doses/unit	0173-0600-02	$74.71
*WAC: wholesale acquisition cost effective 05/31/07 (accessed 08/21/07). WAC is the listed price to wholesalers and warehousing chains, not including prompt pays, stocking or distribution allowances, or other discounts, rebates or charge backs.				

Flovent Diskus is a specially designed plastic inhalation delivery system containing a double-foil blister strip. Each blister contains 50 mcg of microfine fluticasone propionate in 12.5 mg of formulation containing lactose (which contains milk proteins), intended for oral inhalation only. Under standardized in vitro test conditions, *Flovent Diskus* 50 mcg delivers 46 mcg of fluticasone propionate at a flow rate of 60 L/min. from the mouthpiece.

The *Diskus* inhalation unit is the delivery component and is an integral part of the drug product. The *Diskus* has a dose counter that counts down with every dose administered; when 5 doses are remaining, the numbers 5 to 0 appear in red.

4.3 AHFS or Other Drug Classification

AHFS DRUG CLASSIFICATION: 68:04 (Adrenal Corticosteroids) for inhaled fluticasone propionate.

4.4 FDA Approved and Other Studied Indications

Refer to Enclosed Prescribing Information.

4.5 Use in Special Populations

Refer to Enclosed Prescribing Information.

4.6 Pharmacology

PHARMACOLOGY OF FLUTICASONE PROPIONATE

Corticosteroids have been demonstrated to be the most effective anti-inflammatory drugs developed to date for asthma.[1] Fluticasone propionate is a trifluorinated corticosteroid with potent anti-inflammatory activity. *In vitro* assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.[2]

The precise mechanism of action of inhaled corticosteroids, like fluticasone propionate, in asthma is unknown. Corticosteroids have been associated with improvements in most of the pathophysiologic changes associated with asthma such as inhibition of multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) involved in the asthmatic response and the mediators they produce (e.g., histamine, eicosanoids, leukotrienes, and cytokines).[18] In addition, evidence has suggested that ICS may have effects on reversing some aspects of airway remodeling. [19] [20] [21] Due

to their broad effects on airway inflammation and its consequences, corticosteroids are regarded as the preferred treatment for persistent asthma in treatment guidelines. [22]

4.7 Pharmacokinetics/Pharmacodynamics

Table 4. Systemic Exposure/Bioavailability of Fluticasone Propionate

Dose(s)	Subjects	Systemic Exposure/Bioavailability
Flovent HFA		
[23] 220 mcg x 8 inhalations as single dose vs FP CFC. AUC_{0-24} compared.	24 healthy volunteers	Systemic exposure of *Flovent* HFA was 33% lower vs FP CFC inhaler. Relative systemic bioavailability was calculated to be 7%
[24] 88 mcg twice daily vs FP CFC. AUC_{last} compared	13 children with asthma, 4-11 years old	Systemic exposure of *Flovent* HFA was 55% lower vs FP CFC. Relative systemic bioavailability was calculated to be 4.5%.
[25] 440 mcg twice daily with *Volumatic* spacer*	13 healthy volunteers vs 11 adults with asthma & mean FEV_1 54% predicted	Systemic bioavailability for healthy volunteers and adults with asthma was 21.4% and 10.1%, respectively
Flovent Diskus		
[26] 400 mcg single dose	14 healthy volunteers	Systemic bioavailability was 6.7%
AUC = area under the concentration time curve, HFA = hydrofluoroalkane propellant, FP = fluticasone propionate, CFC = chlorofluorocarbon *The efficacy of using *Flovent* with a spacer device has not been established.		

4.8 Contraindications

Refer to Enclosed Prescribing Information.

4.9 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.10 Adverse Events

Refer to Enclosed Prescribing Information.

4.11 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

4.12 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.13 Dosing and Administration

FLOVENT HFA AND *FLOVENT DISKUS* RECOMMENDED DOSING

Both *Flovent* HFA and *Flovent Diskus* should be administered by the orally inhaled route in patients 4 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. After asthma stability has been achieved, it is always desirable to titrate to the lowest effective dosage to reduce the possibility of side effects. For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, higher dosages may provide additional asthma control. The safety and efficacy of *Flovent* when administered in excess of recommended dosages have not been established.

The recommended starting dosage and the highest recommended dosage for *Flovent* HFA were based on prior asthma therapy of the adolescent and adult patients randomized to key clinical trials (Table 5).

Table 5. Recommended Dosages of *Flovent* HFA Inhalation Aerosol(2)

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Patients 4-11 years‡	88 mcg twice daily	88 mcg twice daily
Patients ≥12 years		
Bronchodilators alone	88 mcg twice daily	440 mcg twice daily
Inhaled corticosteroids	88-220 mcg twice daily*	440 mcg twice daily
Oral corticosteroids†	440 mcg twice daily	880 mcg twice daily

*__For Patients Currently Receiving Inhaled Corticosteroid Therapy:__ Starting dosages above 88 mcg twice daily may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

†__For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:__ Prednisone should be reduced no faster than 2.5 to 5 mg/day on a weekly basis, beginning after at least 1 week of therapy with *Flovent* HFA. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency. Once prednisone reduction is complete, the dosage of *Flovent* HFA should be reduced to the lowest effective dosage.

‡Recommended pediatric dosage is 88 mcg twice daily regardless of prior therapy.

The recommended starting dosage and the highest recommended dosage for *Flovent Diskus* were based on prior asthma therapy of the patients randomized to key clinical trials (Table 6).

Table 6. Recommended Dosages of *Flovent Diskus*(10)*

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Children 4 to 11 Years		
Bronchodilators alone	50 mcg twice daily	100 mcg twice daily
Inhaled corticosteroids	50 mcg twice daily	100 mcg twice daily
Patients ≥ 12 Years		
Bronchodilators alone	100 mcg twice daily	500 mcg twice daily
Inhaled corticosteroids	100-250 mcg twice daily	500 mcg twice daily

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Oral corticosteroids†	500-1,000 mcg twice daily‡	1,000 mcg twice daily

*Starting dosages above 100 mcg twice daily for adults and adolescents and 50 mcg twice daily for children 4 to 11 years of age may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

†**For Patients Currently Receiving Chronic Oral Corticosteroid Therapy**: Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with *Flovent Diskus*. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency. Once prednisone reduction is complete, the dosage of *Flovent* should be reduced to the lowest effective dosage.

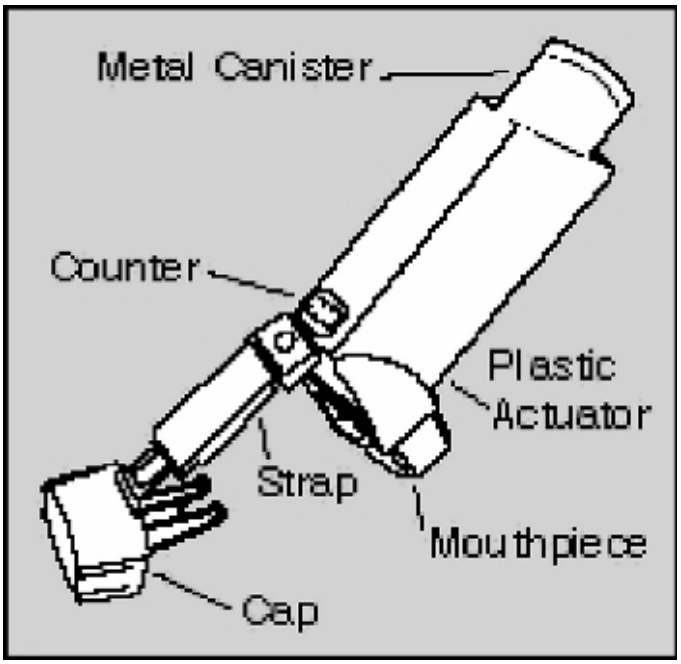
‡The choice of starting dosage should be made on the basis of individual patient assessment. A controlled clinical study of 111 oral corticosteroid-dependent patients with asthma showed few significant differences between the 2 doses of *Flovent Diskus* on safety and efficacy endpoints. However, inability to decrease the dose of oral corticosteroids further during corticosteroid reduction may be indicative of the need to increase the dose of *Flovent* up to the maximum of 1,000 mcg twice daily.

Flovent HFA with Dose Counter

The dose counter on *Flovent* HFA shows the number of inhalations remaining through a window in the back of the inhaler. The number of inhalations starts at number 124 (4 initial priming sprays plus 120 inhalations content) and counts down (mechanically) by 1 each time the inhaler is sprayed. The counter will stop counting when it reaches 000. The correct amount of medication in each inhalation cannot be assured after 000 is reached even though the canister is not completely empty and will continue to operate. The dose counter is fitted onto the metal canister and is not meant to be detached (Figure 1).

The results of a survey of 500 families with asthma showed that patients in these families did not have a reliable way to keep track of the contents of metered dose inhalers.[27] A dose counter may assist patients in getting medication refills at the right time, thus avoiding throwing away a partially used inhaler or continuing to rely on an inhaler after the number of labeled inhalations have been used.

Figure 1. *Flovent* HFA Dose Counter



4.14 Co-prescribed/Concomitant Therapies

Refer to Enclosed Prescribing Information.

5. PIVOTAL EFFICACY AND SAFETY TRIALS

5.1 Pivotal Efficacy and Safety Trails with *Flovent Diskus* in Children 4-11 with Asthma

PIVOTAL TRIALS

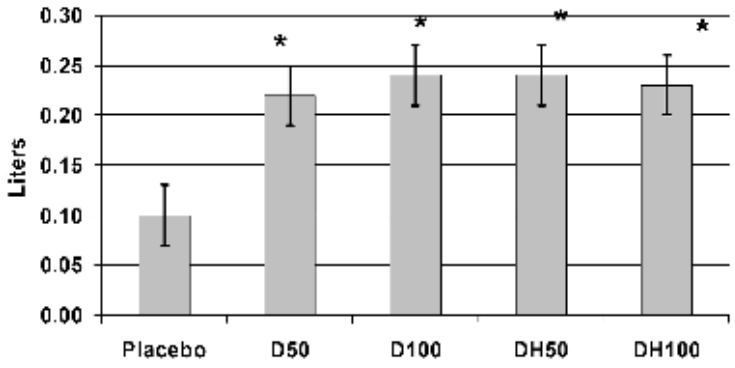
Peden et al conducted a 12-week, randomized, double-blind, parallel-group trial to evaluate the efficacy and safety of *Flovent Diskus* in children with asthma. [11] Children 4 to 11 years old with persistent asthma (mean FEV_1 72%-74% of predicted) were randomized to *Flovent Diskus* or *Flovent Rotadisk*® (fluticasone propionate inhalation powder) 50 mcg or 100 mcg twice daily or placebo (Table 7). Patients were stratified according to their baseline treatment: inhaled corticosteroids, cromolyn, or $beta_2$-agonists alone. *Flovent Rotadisk* is no longer available in the US.

Table 7. *Flovent Diskus:* Baseline Demographics and Characteristics

	50 mcg BID n = 90	**100 mcg BID n = 87**	**Placebo n = 86**
Patients 4-5 Years, %	12	16	8
Patients 6-11 Years, %	88	84	92
FEV_1% predicted	73	74	73
AM PEF, L/min	217	216	226
Asthma symptom score*	0.81	0.80	0.72
Albuterol use, puffs/day	1.61	1.96	1.42
FEV_1 : forced expiratory volume in one second; PEF: peak expiratory flow *Asthma symptom scoring (0 = none, 1 = mild, and 3 = severe).			

Patients treated with *Flovent Diskus* experienced greater improvements in FEV_1 (Figure 2), PEF, albuterol use and nighttime awakenings compared with those treated with placebo (Table 8). Additionally, mean asthma symptoms scores were also significantly decreased at endpoint in all patients treated with *Flovent* versus placebo except for those receiving *Flovent Diskus* 50 mcg. More patients treated with placebo withdrew from the study because of poor control of asthma ($P < 0.001$). Efficacy results were similar for the *Flovent Diskus* and *Flovent Rotadisk* groups.

Figure 2. *Flovent Diskus vs. Diskhaler*: Clinic AM Predose FEV_1 Mean Change at Endpoint



* P≤0.023 vs. Placebo

Table 8. *Flovent Diskus*: Other Results in Children

Mean Change from Baseline at Endpoint	50 mcg BID	100 mcg BID	Placebo
FEV_1 % predicted	11.3*	12.5*	4.7
Clinic AM PEF, L/min	51*	48*	22
Diary AM PEF, L/min	34*†	40*	13
Diary PM PEF, L/min	26*†	34*	12
Asthma symptom score	-0.36	-0.41*	-0.02
Albuterol use, puffs/day	-0.75*	-1.04*	0.08
Awakenings/night	-0.03*	-0.06*	0.07
*$P \leq 0.05$ versus placebo			

Flovent was well tolerated throughout the study. There was no effect on the hypothalamic-pituitary-adrenal (HPA) axis as measured by morning plasma cortisol levels and 24-hour urinary free-cortisol excretion.

A 12-week, randomized, double-blind, placebo-controlled trial compared the safety and efficacy of *Flovent Diskus* 50 mcg twice daily, 100 mcg once daily, and placebo.[28] Patients (N = 262) were 4-11 years of age with a history of asthma requiring regular or as needed asthma medication. Patients were required to have a PEF ≤ 85% of predicted (4-5 years old) or FEV_1 50-85% of predicted (6-11 years old), and ≥ 15% increase in FEV_1 following albuterol (6-11 years old). After a 2-week run-in phase, patients were stratified to treatment based on baseline therapy. The primary efficacy endpoints were clinic AM pre-dose FEV_1 and PEF.

Baseline demographics were similar between treatment groups. The patients were primarily male (60%) with a mean age of 7.6 - 8 years with approximately 20% of the population being 4-5 years of age. Nearly half of the patients were previously receiving an ICS or cromolyn sodium (46%) while the rest had been receiving bronchodilators alone (54%).

Patients on *Flovent Diskus* 50 mcg twice daily had significant improvements in clinic AM PEF, albuterol use, and nighttime awakenings requiring albuterol compared with the placebo group. Numerical improvements in other measures of lung function and asthma symptom scores were observed but were not statistically significant (Table 9). Fewer patients treated with *Flovent Diskus* 50 mcg compared with placebo were withdrawn from the study due to lack of efficacy ($P = 0.014$).

Table 9. *Flovent Diskus*: Results in Children

Mean Change from Baseline at Endpoint	50 mcg BID	100 mcg QD	Placebo
AM Pre-dose FEV_1, L	0.13	0.08	0.05
FEV_1 % predicted	7.4	4.7	3.8
Clinic AM PEF, L/min	38.5*	26.0	10.7
Clinic AM PEF % predicted	17.0*	10.5	5.85
Diary AM PEF, L/min	21	25	12
Diary PM PEF, L/min	20*	25*	9
Asthma symptom scores	-0.3	-0.24	-0.08
Albuterol use, puffs/day	-0.98*	-0.56	0.07
Nighttime awakenings requiring albuterol	-0.04*	-0.03*	0.05
Withdrew due to lack of efficacy, %	19*	25	35
*$P < 0.05$ versus placebo			

Both regimens of *Flovent Diskus* were well-tolerated during the study. Safety profiles including adverse events, AM cortisol, oropharyngeal examinations, and vital signs were similar to that of the placebo group.

CLINICAL SAFETY PROFILE

The incidence of common adverse events is based upon placebo-controlled US clinical trials in which pediatric (3 studies), adolescent and adult (4 studies) patients previously treated with as needed bronchodilators and/or inhaled corticosteroids were treated with *Flovent Diskus* 50 to 500 mcg twice daily or placebo for up to 12 weeks (Table 10).[10] All events whether considered drug-related or non-drug-related by the investigator were included. In considering these data, differences in average duration of exposure should be taken into account These adverse events were mostly mild to moderate in severity, with <2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

Table 10. *Flovent Diskus*: Overall Adverse Events With >3% Incidence in US Trials

Adverse Event, %	Placebo n = 543	50 mcg n = 178	100 mcg n = 305	250 mcg n = 86	500 mcg n = 64
Ear, nose and throat					
Upper respiratory tract infection	16	20	18	21	14
Throat irritation	8	13	13	3	22
Sinusitis/sinus infection	6	9	10	6	6
Upper respiratory inflammation	3	5	5	0	5
Rhinitis	2	4	3	1	2
Oral candidiasis	7	<1	9	6	5
Gastrointestinal					
Nausea and vomiting	4	8	4	1	2
Gastrointestinal discomfort/pain	3	4	3	2	2
Viral gastrointestinal infection	1	4	3	3	5
Non-site specific					
Fever	4	7	7	1	2
Viral Infection	2	2	2	0	5
Lower respiratory					
Viral respiratory infection	4	4	5	1	2
Cough	4	3	5	1	5
Bronchitis	1	2	3	0	8
Neurological					
Headache	7	12	12	2	14
Musculoskeletal and trauma					
Muscle injury	1	2	0	1	5
Musculoskeletal pain	2	4	3	2	5
Injury	<1	2	<1	0	5
Average exposure, days	56	76	73	79	78

5.2 Pivotal Efficacy and Safety Trials with *Flovent Diskus* in Adults and Adolescents with Asthma

Patients previously treated with bronchodilators alone or inhaled corticosteroids (ICS)

Wolfe et al reported the pooled results of two 12-week, randomized, double-blind, double-dummy, parallel-group studies comparing the efficacy and safety of *Flovent Diskus* 100 mcg twice daily, 200 mcg once daily, and placebo. [13] Patients in the first study were previously treated with bronchodilators alone (N = 223), had a FEV_1 68% of predicted, and used from 2.3 to 2.7 puffs of albuterol per day. The patients

in the second study were previously treated with ICS (N = 199), had a FEV_1 66% to 68% of predicted, and had used from 2.6 to 2.9 puffs of albuterol per day. Results showed that the percentage of bronchodilator patients withdrawn from the first study for lack of meeting predefined efficacy criteria was much higher in the placebo group (26%) compared with the *Flovent* BID and QD groups (7% and 9%, respectively). In the second study, 48% , 18%, and 32% of patients in the placebo, *Flovent* BID and QD groups were withdrawn (*Flovent* groups vs. placebo; $P \leq 0.045$). There were no statistically significant differences in either study between the *Flovent* BID and QD groups. Pulmonary function and asthma symptom improvements were also generally greater in the groups receiving *Flovent Diskus* (Table 11).

Table 11. *Flovent Diskus*: Mean Change from Baseline at Endpoint

	Placebo	100 BID	200 QD
FEV_1, L			
Bronchodilator	0.21	0.49*	0.37*
ICS	-0.08	0.27*	0.11*
FEV_1 % of predicted			
Bronchodilator	5.28	12.77*	9.45
ICS	-2.10	7.24*	2.59*
AM PEF, L/min			
Bronchodilator	1	31*	27*
ICS	-12	18*†	-3
PM PEF, L/min			
Bronchodilator	5	25*	26*
ICS	-7	15*	0
Asthma symptom score			
Bronchodilator	-0.12	-0.4*	-0.37
ICS	0.14	0.23*†	-0.03*
Albuterol use, puffs/day			
Bronchodilator	0.22	-1.07*	-0.82*
ICS	1.29	-0.43*	-0.11*
Nighttime awakenings			
Bronchodilator	-0.03	-0.06	-0.06
ICS	0.07	-0.01	-0.01

*$P \leq 0.05$ vs. Placebo; †$P < 0.05$ vs. *Flovent* once daily; Asthma symptom scoring, 0 = none to 3 = severe

ZuWallack et al [14] evaluated the long-term efficacy and safety of *Flovent Diskus* in 253 patients 12-69 years old with moderate asthma and a mean FEV_1 67% of predicted. Patients were stratified according to baseline therapy of bronchodilators alone or ICS. During the initial 12-week, double-blind, parallel-group phase, eligible patients were randomized to receive *Flovent* 250 mcg twice daily, 500 mcg once daily, or placebo. During the 54-week open-label phase, patients were re-randomized to once-daily or twice-daily *Flovent*.

During the double-blind phase, the mean change in FEV_1 at endpoint was 0.42 L and 0.12 L after *Flovent* 250 mcg twice daily and 500 mcg once daily, respectively, compared with a mean decrease of –0.16 L after placebo ($P < 0.001$ for both *Flovent* groups vs. placebo; $P \leq 0.05$ for *Flovent* 250 mcg twice daily vs.

500 mcg once daily). At endpoint, both *Flovent* regimens resulted in significant improvements ($P<0.001$) in morning and evening PEF compared with placebo; there was no significant difference between once and twice daily regimens. Significantly more patients treated with placebo were withdrawn due to lack of efficacy (51%) compared with patients treated with *Flovent* 250 mcg twice daily (7%; $P<0.001$ vs. placebo and 500 mcg once daily) and *Flovent* 500 mcg once daily (26%; $P = 0.001$ vs. placebo). Both regimens significantly improved ($P\leq0.001$) asthma symptom scores and significantly reduced ($P \leq0.001$) rescue albuterol use compared with placebo; the reduction in rescue albuterol use was also significantly greater ($P = 0.045$) in the twice daily group compared with once daily group. During the open-label phase, patients in both groups either maintained or continued to improve in FEV_1 measurements. Patients previously treated with placebo had large improvements in FEV_1 (0.43-0.83 L) beginning as early as 2 weeks and maintained throughout the 54-week phase.

Flovent was well tolerated throughout the study. Following 12 weeks of double-blind treatment, abnormal morning plasma cortisol concentrations were reported in 1%, 8%, and 3% of patients treated with placebo, 250 mcg twice daily, and 500 mcg once daily, respectively. After the 54-week extension, abnormal morning plasma cortisol concentrations were reported in 0%, 5%, and 7% of patients treated with placebo, 250 mcg twice daily, and 500 mcg once daily, respectively. Cosyntropin stimulation testing identified one patient in the once daily group who had an abnormal response.

The safety and efficacy of *Flovent Diskus* was studied in a 12-week, randomized, double-blind, double-dummy, parallel-group study reported by Galant et al. [15] Two hundred thirteen adolescent and adult patients with mild to moderate persistent asthma (FEV_1 65% to 67% of predicted) were randomized to *Flovent Diskus* or *Flovent Rotadisk* (*Diskhaler* device) 500 mcg twice daily or placebo groups. Patients were also stratified according to treatment at baseline of inhaled corticosteroids (ICS) or bronchodilators alone.

Pulmonary function improved in all patients who received either formulation of *Flovent*, regardless of treatment at baseline. Overall, efficacy results were similar between *Flovent Diskus* and *Flovent Rotadisk*. FEV_1 ($P<0.001$), morning and evening peak expiratory flow (PEF) ($P<0.001$), asthma symptom scores ($P<0.016$), and rescue albuterol use ($P<0.001$) were improved at endpoint in patients receiving *Flovent* compared with placebo. Nighttime awakenings were significantly reduced in patients receiving *Flovent Rotadisk* compared with placebo at endpoint ($P = 0.016$). More patients treated with placebo (34%) than with *Flovent Diskus* (5%) or *Flovent Rotadisk* (5%) withdrew from the study due to lack of efficacy ($P<0.01$). Unstimulated morning plasma cortisol concentrations were not significantly affected by *Flovent Diskus* or *Flovent Rotadisk* vs. placebo.

CLINICAL SAFETY PROFILE

The incidence of common adverse events is based upon placebo-controlled US clinical trials in which pediatric (3 studies), adolescent and adult (4 studies) patients previously treated with as needed bronchodilators and/or inhaled corticosteroids were treated with *Flovent Diskus* 50 to 500 mcg twice daily or placebo for up to 12 weeks ().[10] All events whether considered drug-related or non-drug-related by the investigator were included. In considering these data, differences in average duration of exposure should be taken into account These adverse events were mostly mild to moderate in severity, with <2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

5.3 Pivotal Efficacy and Safety Trials with *Flovent HFA* in Adults and Adolescents with Asthma

PIVOTAL TRIALS

Three randomized, double-blind, parallel-group, placebo-controlled clinical trials were conducted in the US in 980 adolescent and adult patients ≥ 12 years of age with asthma to assess the efficacy and safety of *Flovent* HFA. Fixed dosages of 88 mcg, 220 mcg, and 440 mcg twice daily (each dose administered

as 2 inhalations of the 44 mcg, 110 mcg, and 220 mcg strengths, respectively) and 880 mcg twice daily (administered as 4 inhalations of the 220 mcg strength) were compared with placebo to provide information about appropriate dosing to cover a range of asthma severity. In all 3 studies, patients (including placebo-treated patients) were allowed to use albuterol via metered dose inhaler as needed for relief of acute asthma symptoms. In Studies 1 and 2, other maintenance asthma therapies were discontinued.

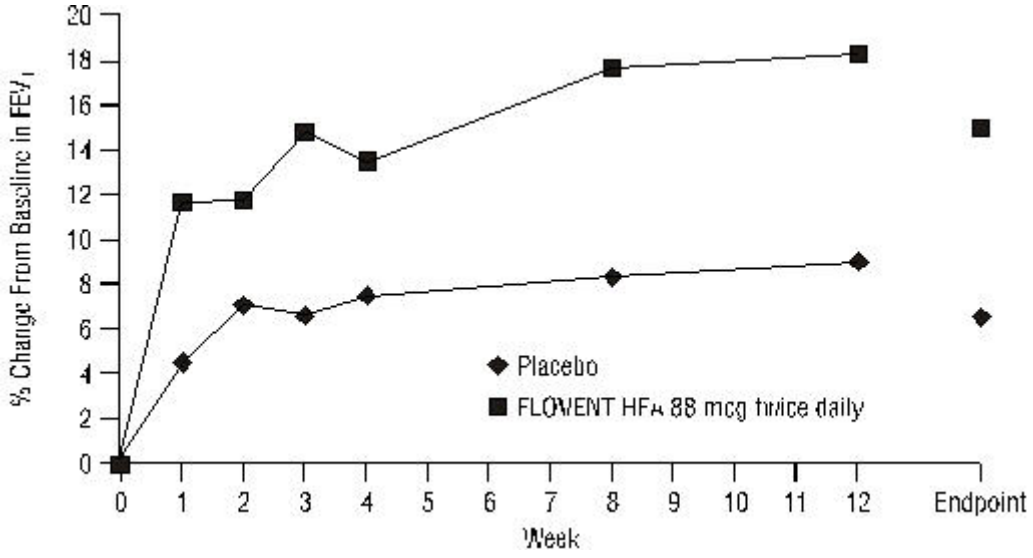
A total of 73 patients between the ages of 12 to 17 years of age were studied in the above pivotal trials. Improved asthma control as measured by an improvement in FEV_1 was greater for patients treated with *Flovent* HFA compared to those treated with placebo.

STUDY 1: PATIENTS INADEQUATELY CONTROLLED WITH BRONCHODILATORS ALONE

Flovent HFA was evaluated at dosages of 88, 220, and 440 mcg twice daily for 12 weeks in 397 patients with asthma inadequately controlled on bronchodilators alone. [3] Baseline FEV_1 values were similar across groups (mean 67% of predicted normal). All 3 dosages of *Flovent* HFA significantly improved asthma control as measured by improvement in AM pre-dose FEV_1 compared with placebo. AM pre-dose FEV_1 improved significantly with *Flovent* HFA compared with placebo after the first week of treatment, and this improvement was maintained over the 12-week treatment period.

At end point (last observation), mean change from baseline in AM pre-dose percent predicted FEV_1 was significantly greater (95% CI) in all 3 groups treated with *Flovent* HFA (9.0% to 11.2%) compared with the placebo group (3.4%). Predetermined criteria for lack of efficacy (indicators of worsening asthma) resulted in withdrawal of more patients in the placebo group. End point was the last evaluable FEV_1 value (Figure 3).

Figure 3. Mean Percent Change From Baseline in FEV1 Prior to AM Dose in a 12-Week Clinical Trial in Patients Inadequately Controlled on Bronchodilators Alone



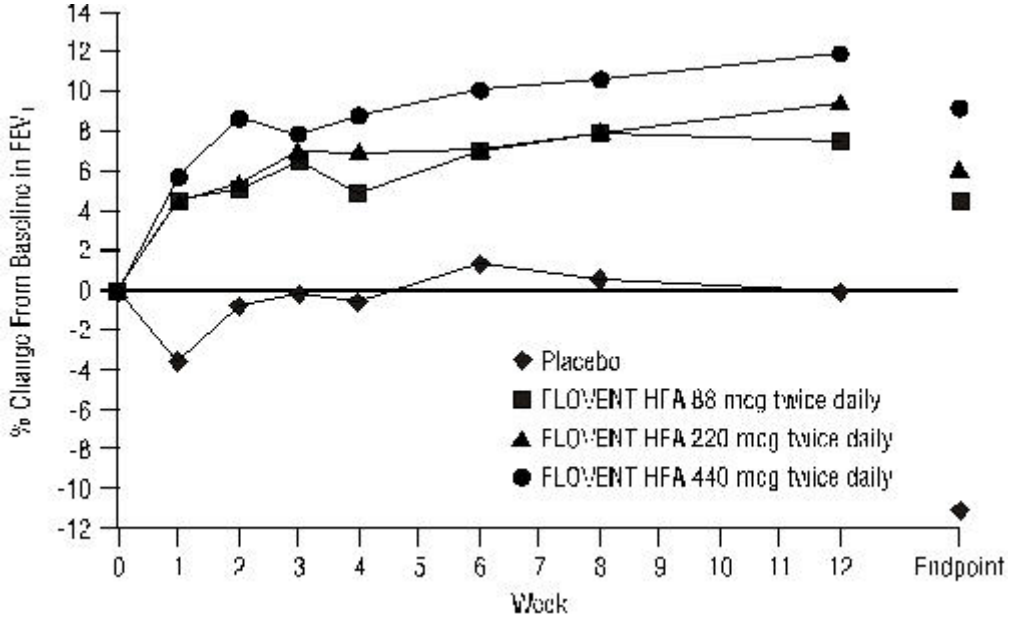
STUDY 2: PATIENTS ALREADY RECEIVING INHALED CORTICOSTEROIDS

Flovent HFA at dosages of 88, 220, and 440 mcg twice daily was evaluated over 12 weeks of treatment in 415 patients with asthma who were already receiving an inhaled corticosteroid at a daily dose within its recommended dose range in addition to as-needed albuterol. [29] Baseline FEV_1 values were similar across groups (mean 65% to 66% of predicted normal). All 3 dosages of *Flovent* HFA significantly improved asthma control as measured by improvement in FEV_1 compared with placebo. Discontinuations from the study for lack of efficacy (defined by a pre-specified decrease in FEV_1 or PEF, or an increase in use of albuterol or nighttime awakenings requiring treatment with albuterol) were lower in the groups treated with *Flovent* HFA (6% to 11%) compared with placebo (50%). AM pre-dose FEV_1 improved significantly

with *Flovent* HFA compared with placebo after the first week of treatment, and the improvement was maintained over the 12-week treatment period.

At endpoint, mean change from baseline in AM pre-dose percent predicted FEV_1 was significantly greater in all 3 groups treated with *Flovent* HFA (2.2% to 4.6%) compared with the placebo group (-8.3%). Predetermined criteria for lack of efficacy resulted in withdrawal of more patients in the placebo group (Figure 4).

Figure 4. Mean Percent Change in FEV_1 Prior to AM Dose in a 12-Week Clinical Trial With Patients Already Receiving Daily Inhaled Corticosteroids

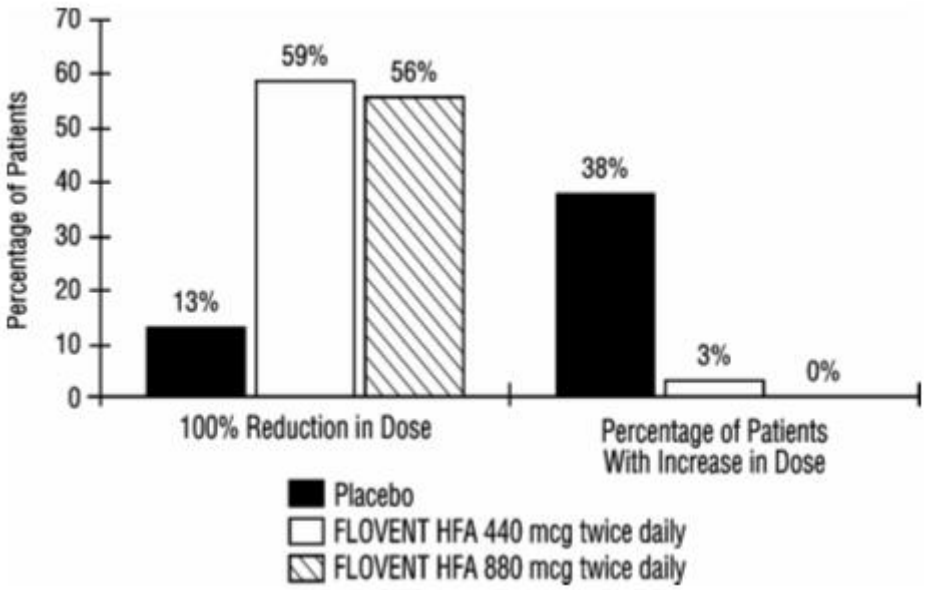


In both studies, use of albuterol, AM and PM PEF, and asthma symptom scores showed numerical improvement in those receiving *Flovent* HFA compared with placebo.

STUDY 3: PATIENTS REQUIRING ORAL CORTICOSTEROID THERAPY

Flovent HFA 440 and 880 mcg twice daily were evaluated over a 16-week treatment period in 168 patients with asthma requiring oral prednisone therapy (average baseline daily prednisone dose ranged from 13 to 14 mg). [30] Baseline FEV_1 values were similar across groups (mean 59% to 62% of predicted normal). Over the course of the study, patients treated with either dosage of *Flovent* HFA required a significantly lower mean daily oral prednisone dose (6 mg) compared with placebo-treated patients (15 mg). Both dosages of *Flovent* HFA enabled a larger percentage of patients (59% and 56% in the groups treated with *Flovent* HFA 440 and 880 mcg, respectively, twice daily) to eliminate oral prednisone as compared with placebo (13%) (Figure 5). There was no efficacy advantage of *Flovent* HFA 880 mcg twice daily compared with 440 mcg twice daily. Accompanying the reduction in oral corticosteroid use, patients treated with either dosage of *Flovent* HFA had significantly improved lung function, fewer asthma symptoms, and less use of albuterol compared with the placebo-treated patients.

Figure 5. Change in Maintenance Prednisone Dose in a 16-Week Clinical Trial in Patients Requiring Chronic Oral Prednisone Therapy



Adverse events reported by >3 patients in either group treated with *Flovent* HFA and more commonly than in the placebo group included rhinitis, nausea and vomiting, arthralgia and articular rheumatism, musculoskeletal pain, muscle pain, malaise and fatigue, and sleep disorders. (30)

SAFETY DATA FROM STUDIES 1 AND 2

The incidence of common adverse events is based upon 2 placebo-controlled US clinical trials (Studies 1 and 2) in which 812 adolescent and adult patients (457 females and 355 males) previously treated with as needed bronchodilators and/or inhaled corticosteroids were treated with *Flovent* HFA 88, 220, or 440 mcg twice daily for up to 12 weeks or placebo (Table 12). (2) The table includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in any of the groups treated with *Flovent* HFA and were more common than in the placebo group. These adverse events were mostly mild to moderate in severity.

Table 12. Adverse Events in Study 1 and 2 Having >3% Incidence in US Trials Using *Flovent* HFA in Patients With Asthma Previously Receiving Bronchodilators and/or ICS[2]

Adverse Event, %	*Flovent* HFA 44 mcg (n = 203)	*Flovent* HFA 110 mcg (n = 204)	*Flovent* HFA 220 mcg (n = 202)	Placebo (n = 203)
Ear, nose, and throat				
Upper respiratory tract infection	18	16	16	14
Throat irritation	8	8	10	5
Upper respiratory inflammation	2	5	5	1
Sinusitis/sinus infection	6	7	4	3
Hoarseness/dysphonia	2	3	6	<1
Gastrointestinal				
Candidiasis mouth/throat & non-site specific	4	2	5	<1
Lower respiratory				
Cough	4	6	4	5
Bronchitis	2	2	6	5
Neurological				
Headache	11	7	5	6

LONG-TERM SAFETY

Two long-term safety studies were conducted in 507 adolescent and adult patients with asthma. One 26-week study was designed to monitor the safety of *Flovent* HFA 220 and 440 mcg twice daily in 89 and 93 patients, respectively, who were treated daily with low to high doses of inhaled corticosteroids, $beta_2$-agonists (short-acting [as needed or regularly scheduled] or long-acting), theophylline, inhaled cromolyn or nedocromil sodium, leukotriene receptor antagonists, or 5-lipoxygenase inhibitors at baseline.[31]

The second long-term study compared *Flovent* HFA and CFC.[32] *Flovent* HFA 440 mcg twice daily and *Flovent* CFC 440 mcg twice daily, with or without concurrent use of salmeterol or albuterol at baseline, were evaluated over a 52-week treatment period in 163 and 162 patients, respectively. Baseline FEV_1 values were similar across groups (mean 81% to 84% of predicted normal). Throughout the study, asthma control was significantly improved with both formulations of fluticasone propionate compared to baseline.

In both studies, none of the patients were withdrawn due to lack of efficacy. Treatment with *Flovent* HFA was well tolerated. Adverse events were similar to that observed in the 12-week studies. There were no new and/or unexpected adverse events with long-term treatment.

5.4 Pivotal Efficacy and Safety Trials with *Flovent HFA* in Children 4-11 with Asthma

CLINICAL INFORMATION

The safety and efficacy of *Flovent* HFA in children 4-11 years of age was evaluated in a randomized, double-blind, parallel-group trial. [5] The study included 241 children with asthma (≥6 months history)

requiring pharmacotherapy, PEF ≤85% of predicted and ≥12% reversibility. Treatment regimens were *Flovent* HFA 88 mcg twice daily (n = 160) or placebo (n = 81) for 12 weeks (Table 13). The primary end point was mean change from baseline in morning pre-dose percent predicted PEF.

Table 13. Baseline Patient Characteristics[5]

Mean Scores	***Flovent* HFA**	**Placebo**
PEF, % predicted, L/min	74.3	73.9
FEV_1 % predicted, L	84.6	85
Duration of asthma, years	5.3	5.4
Asthma severity classification*	8%, 13%, 28%, 51%	15%, 9%, 30%, 47%
*NHLBI classification of disease severity: mild intermittent, mild persistent, moderate persistent, severe persistent, respectively		

Flovent HFA significantly improved the mean change in AM pre-dose percent predicted PEF compared with placebo, independent of pre-study inhaled corticosteroid use (approximately half of each group) (Table 14). Patients receiving *Flovent* HFA also had greater improvements in all other efficacy measurements except asthma symptom score.

Table 14. Mean Change from Baseline [5]

Least Square Mean Change	***Flovent* HFA**	**Placebo**	**P-value**
Clinic AM pre-dose % predicted PEF	10.1	3.9	0.003
Clinic % predicted FEV_1 (ages 6-11 only)	0.95	-2.11	0.050
Diary morning PEF (L/min)	18.1	5.2	0.001
Diary evening PEF (L/min)	15.2	6.8	0.031
Diary asthma symptom score*	-0.32	-0.18	0.176
Diary rescue albuterol use (puffs/day)	-0.5	0.08	<0.001
Albuterol-free days (post-hoc)	21.55%	7.80%	0.004
Diary nighttime awakenings	0	0.09	0.008
At least a 2-step improvement in asthma severity or improvement to mild intermittent severity (post-hoc), % patients	30%	16%	0.028
*Asthma symptoms per 24 hours (cough, wheeze, shortness of breath, chest tightness) rated on a 6-point scale from 0 (none) to 5 (so severe that work or normal daily activities could not be performed). Clinic visits were at weeks 1, 2, 4, 8 and 12.			

Flovent HFA was well-tolerated. Drug-related adverse events were reported in 5% of patients in the *Flovent* HFA group and 2% of placebo patients. There was no evidence of adrenal suppression. Median changes in 12-hour overnight urinary cortisol excretion for *Flovent* HFA (baseline 3.5 mcg to -0.1 mcg end point) and the placebo group (baseline 3.1 mcg to 0.1 mcg end point) were similar. Vitals signs and clinical laboratory results were also similar between groups.

Effect on the Hypothalamic-Pituitary-Adrenal (HPA) Axis

The effect of *Flovent* HFA on 24-hour urinary excretion of cortisol was evaluated in a 6-week, open-label study in 40 children 4 to 11 years of age with asthma. [33] The patients were administered placebo HFA inhaler for 2 weeks, followed by treatment with *Flovent* HFA 88 mcg twice daily for 4 weeks. Twenty-four

hour urine collections were conducted at the end of both the placebo and *Flovent* HFA phases. Urinary cortisol (urinary cortisol + 6-beta-hydroxycortisol) levels were not affected by the administration of *Flovent* HFA compared with placebo. The ratio of urinary cortisol and the ratio of urinary cortisol plus 6-beta-hydroxycortisol excreted over 24 hours after treatment with *Flovent* HFA were 0.987 (95% CI 0.796-1.223) and 0.829 (95% CI 0.685-1.004), respectively.

6. ADDITIONAL SAFETY INFORMATION

6.1 Studies Assessing the Effect on Hypothalamic-Pituitary-Adrenal Axis in Adults and Adolescents

EFFECT ON HPA IN ADOLESCENTS AND ADULTS WITH ASTHMA

Flovent via metered-dose inhaler (HFA or CFC MDI) or a dry powder formulation (*Rotadisk*® or *Diskus*®) has been studied in adolescents and adults with asthma. The criteria used for study inclusion were: 1) HPA axis effect of *Flovent* was a primary endpoint; 2) ACTH stimulation tests assessed HPA axis effects; and 3) treatment durations were at least 4 weeks.

Flovent has been compared with placebo, beclomethasone dipropionate, budesonide, triamcinolone acetonide, flunisolide, mometasone furoate, and oral corticosteroids in studies 4 weeks to 2 years in duration.

FLOVENT COMPARED WITH PLACEBO IN ADULTS WITH ASTHMA

As observed with other inhaled corticosteroids (ICS), HPA axis effects with *Flovent* were dose-dependent. At doses up to 500 mcg per day, patients receiving *Flovent* had no clinically significant effect on HPA axis function (Table 15).

Table 15. *Flovent*: HPA Axis Effect Compared with Placebo in Adults with Asthma

Design, Baseline Corticosteroids	6-hour Cosyntropin Stimulation Test (CST)
[34] 2 years, DB, randomized, placebo-controlled, parallel-group; N = 64, 18-49 years old, no corticosteroids within 1 month; ≤4 weeks cumulative oral corticosteroids; and ≤1 year cumulative corticosteroids from any route. *Flovent* powder 500 mcg BID (*Diskhaler*)	Measured every 6 months: Peak cortisol concentration: minor, but significant (P = 0.021) decrease at week 104 in the FP vs. PL group. Abnormal: 1 patient (PL) and 5 patients (FP); 4 had normal subsequent tests. 8-hour plasma cortisol AUC: minor but significant (P = 0.020) decrease week 104 in the FP vs. PL group. No progressive decline in HPA axis function was observed over 2 years.
[35] 2 years, DB, randomized, placebo-controlled, parallel-group N = 160; no oral corticosteroids within 1 month; ≤3 years cumulative total corticosteroids of any type. *Flovent* 88, 440 mcg BID MDI	Measured every 6 months: Peak cortisol concentration; 1 patient (PL), 2 patients (FP 88), and 7 patients (FP 440) had abnormal peak cortisol.
[36] 4 weeks, randomized, placebo-controlled; N = 97, 18-50 years old; minimal recent corticosteroid exposure. *Flovent* 250, 500, 750, 1000 mcg BID, MDI	FP 250 mcg: no patient had an abnormal peak cortisol concentration. *Flovent* 500, 750, & 1000 mcg: 10%, 16%, & 12% of patients, respectively, exhibited an abnormal peak cortisol.
BID = twice daily; HPA = hypothalamic pituitary adrenal; MDI = metered dose inhaler	

***Flovent* Compared with Beclomethasone Dipropionate & Budesonide in Adults with Asthma**

Flovent 500 - 1000 mcg daily demonstrated significantly less suppressive effects on HPA axis function compared with beclomethasone dipropionate 1000 - 2000 mcg. Patients receiving *Flovent* 400 - 1500 or budesonide 400 - 1600 mcg daily had similar effects on the HPA axis (Table 16).

Table 16. *Flovent* Compared with Beclomethasone Dipropionate MDI & Budesonide in Adults with Asthma

Study Design, Baseline Corticosteroid	ACTH Stimulation Cortisol
[37] 4 months, double-blind, randomized, crossover. N = 67, mean age 48 years old. BDP 1 mg per day, no oral corticosteroids within 3 months.*Flovent* CFC 500, 1000 mcg or BDP CFC 1, 2 mg MDI	Peak cortisol concentration (cosyntropin): *Flovent* had larger increase vs. BDP (P<0.01)
[38] 24 weeks, open-label, randomized, parallel-group. N = 109, 18-69 years old, BUD 400 or BDP 800 mcg/day. *Flovent* powder 1500 mcg/day (Diskhaler) or BUD 1600 mcg/day (Turbuhaler); doses reduced to 800 (after 8 weeks) and 400 mcg/day (after 16 weeks)	Cortisol conc: no difference between groups. Number of patients with subnormal response: FP (n = 18), BUD (n = 13)
[39] 8 weeks, double-blind, randomized, parallel-group. N = 57 adults, receiving mean 825 mcg per day, mainly BDP. *Flovent* 375 mcg BID, CFC MDI or BUD 400 mcg BID (Turbuhaler)	24-hour integrated plasma cortisol AUC: No statistically significant difference between treatment groups.
BID = twice daily; BUD = budesonide; HPA = hypothalamic pituitary adrenal; MDI = metered dose inhaler' BDP = beclomethasone dipropionate; ICS is inhaled corticosteroid	

Flovent Compared with Triamcinolone Acetonide in Adults with Asthma

In randomized, double-blind, placebo-controlled studies, *Flovent* demonstrated similar to significantly less suppressive effects on HPA axis function compared with triamcinolone acetonide (Table 17).

Table 17. HPA Axis Effect of *Flovent* (FP) Compared with Triamcinolone Acetonide in Adults with Asthma

Study Design, Baseline Corticosteroid	6-Hour Cosyntropin Stimulation Test (CST) 250 mcg
(40) 4 weeks, double-blind, double-dummy, randomized, placebo-controlled, parallel-group. N = 137, 18-51 years old. Minimal use of corticosteroids and no ICS prior 90 days *Flovent* 100 or 500 mcg BID *Diskhaler*; TAA 300 or 500 mcg BID, CFC MDI with spacer.	8-hour plasma cortisol AUC, mean & % change from baseline: FP 100 or FP 500 vs. PL, no difference for either measure. Larger change for TAA 500 vs. PL; P = 0.019, P = 0.042, respectively. Less change for FP 500 vs. TAA 300; *P* = 0.043, *P* = 0.048, respectively. Mean peak plasma cortisol, mean & % change from baseline: no difference for FP 100 or FP 500 vs. PL. TAA 500 larger decrease vs. PL & TAA 300; *P* = 0.034 & *P* = 0.019, respectively. Mean 12-hour plasma cortisol concentration similar across groups except for FP 100 vs. FP 500 (hour 4), FP 100 vs. TAA 500 (hours 4, 10, 12), FP 500 vs. TAA 500 (hours 10, 12). Number of patients with abnormal response: FP 100 or 500 (n = 0), TAA (n = 1), PL (n = 0)
(41) 28 days, double-blind, double-dummy, randomized, placebo-controlled, parallel-group. N = 103, 18-53 years. No corticosteroids (all routes) prior 4 weeks *Flovent* 88, 220 mcg BID, CFC MDI or TAA 200 mcg QID or 400 mcg BID, CFC MDI with spacer	8-hour plasma cortisol AUC, mean or % change from baseline: FP 88 or FP 220 vs. PL: no significant differences. TAA 400 larger vs. PL: *P* = 0.028 & *P* = 0.022, respectively. TAA 400 larger vs. FP 8; *P* = 0.023 & *P*= 0.021, respectively. Peak plasma cortisol, mean or % change from baseline: FP 88 or FP 220 vs. PL; similar change. TAA 400 greater change vs. PL (*P*<0.027). TAA 400 greater change vs. FP 88 (*P*<0.013.) Mean 12- hour plasma cortisol concentration: similar across groups. Number of patients with abnormal response: FP 200 (1 patient), FP 88 (none), TAA (none), PL (none)
(42) 4 weeks, double-blind, double-dummy, randomized, placebo-controlled. N = 120, 18-50 years old. Minimal prior use and no corticosteroids within last 3 months *Flovent* 88 or 220 mcg BID, CFC MDI; TAA 200 mcg QID or 400 mcg BID, CFC MDI.	12-hour plasma cortisol AUC : no difference for FP vs. TAA or PL, or TAA vs. FP or PL. Number of patients with abnormal response: FP 200 (n = 1), FP 88 (n = 0), TAA 200 or 400 (n = 0)
BID = twice daily; HPA = hypothalamic pituitary adrenal; MDI = metered dose inhaler; QID = four times a day; TAA = triamcinolone acetonide; CFC = chlorofluorocarbon propellant	

Flovent Compared with Flunisolide and Mometasone Furoate in Adults with Asthma

Flovent 100 mcg and 250 mcg twice daily and flunisolide 500 mcg twice daily had no differences on HPA axis measurements in a randomized, double-blind, placebo-controlled study (Table 18). Patients receiving

Flovent 880 mcg twice daily and mometasone furoate 400 and 800 mcg twice daily had normal responses to ACTH stimulation after 28 days in a single-blind, randomized, placebo-controlled study.

Table 18. *Flovent* Compared with Flunisolide and Mometasone Furoate in Adults with Asthma

Study Design, Baseline Corticosteroid	Cosyntropin Stimulation Test (CST)
(40) 4 weeks, double-blind, double-dummy, randomized, placebo-controlled, parallel-group. N = 119, 18-51 years old. Minimal exposure to corticosteroids, no ICS for 90 days. *Flovent* 100, 250 mcg BID (*Diskhaler*) or FLN 500 mcg BID, CFC MDI	6-hour CST (250 mcg): 8-hour plasma cortisol AUC, peak plasma cortisol, mean 12-hour plasma cortisol concentration: no statistically significant differences among FP, FLN, and PL. Number of patients with abnormal peak cortisol concentration: FLN (n = 1) FP (n = 0), PL (n = 0)
(43) 28 days, SB (evaluator), randomized, placebo-controlled, parallel-group. N = 64, 19-50 years old. No oral corticosteroids prior 6 months; no IM prior year; no ICS prior to study. *Flovent* 880 mcg BID, CFC MDI; MF 400 or 800 mcg BID, MDI	CST (250 mcg intramuscularly): Weekly mean 24-hour cortisol AUC was lower for FP 880 vs. PL ($P<0.01$). MF 800 vs. PL: lower weeks 2, 3, 4 ($P<0.05$). FP 880 vs. MF 800: lower, but data not reported. Number of patients with abnormal response day 29: none
BID = twice daily; FLN = flunisolide CFC; HPA = hypothalamic pituitary adrenal; MDI = metered dose inhaler; MF = mometasone furoate; SB = single blind; CFC = chlorofluorocarbon propellant, ICS = inhaled corticosteroids; IM: intramuscular	

Flovent Compared with Oral Corticosteroids in Adults with Asthma

Patients receiving Flovent ≤ 2000 mcg per day had less effect on the HPA axis compared with oral prednisone 10 mg daily (Table 19). After 3-4 years of treatment with Flovent 1000-2000 mcg per day, 63% of patients who were previously dependent on oral corticosteroids responded normally to ACTH stimulation testing.

Table 19. *Flovent* (FP) Compared with Oral Corticosteroids on Effect on HPA Axis in Adults with Asthma

Study Design, Baseline Corticosteroid	Cosyntropin Stimulation Test (CST)
[36] 28 days, randomized, placebo-controlled. N = 118, 18-50 years old. Minimal recent corticosteroid exposure. FP 250, 500, 750, 1000 mcg BID, CFC MDI; prednisone 10 mg orally daily	6-hour CST: no patient had an abnormal peak cortisol concentration in the FP 250 mcg or PL groups Percent of patients with abnormal conc: FP 500 (10%), 750 (16%), 1000 mcg (12%), prednisone (29%).
[40] 4 weeks, double-blind, double-dummy, randomized, placebo-controlled, parallel-group. N = 165, 18-51 years old. Minimal prior exposure to corticosteroids; no ICS for 90 days. FP 100 or 250 mcg BID (*Diskhaler*) or prednisone 10 mg orally daily	6-hour CST (250 mcg): Peak plasma cortisol conc, 8-hour plasma cortisol AUC, mean and % change from baseline: significantly greater decreases for prednisone vs. FP (P<0.001). Mean 12-hour plasma cortisol concentration significantly reduced for prednisone vs. FP (P<0.03). Number of patients with abnormal response: prednisone (n = 3, abnormal peak) and FP (n = 0)
[42] 4 weeks, double-blind, double-dummy, randomized, placebo-controlled. N = 98, 18-50 years old. Minimal prior exposure and no corticosteroids prior 3 months. FP 88 or 220 mcg BID, CFC MDI; prednisone 10 mg orally daily	6-hour CST (250 mcg): 12-hour plasma cortisol AUC was greater for FP 88 or 220 vs. prednisone (P<0.001) Mean peak cortisol concentration greater for FP 88 or 220 vs. prednisone (P<0.001).
[44] 3-4 years, open-label, follow-up to trial. [45]N = 51, 28-82 years old. Steroid-dependent on daily prednisone 10 mg for ≥ 6 months. 95%, 90%, & 91% of patients in PL, FP 750, FP 1000 groups, respectively, had abnormal baseline AM cortisol. *Flovent* 250 - 1000 mcg BID, CFC MDI tested.	CST (250 mcg): FP 1000-2000 mcg daily: 63% of patients previously steroid –dependent responded normally and none exhibited clinical signs of adrenal suppression. 98% of patients had stopped regularly scheduled prednisone. 78% had not used regularly scheduled or intermittent prednisone during the last 9-12 months.
BID = twice daily; HPA = hypothalamic pituitary adrenal; MDI = metered dose inhaler; CFC = chlorofluorocarbon propellant, PL = placebo	

6.2 Studies Assessing the Effect on Hypothalamic-Pituitary-Adrenal Axis in Children

PUBLISHED INFORMATION

The effect on the HPA axis was evaluated in children with asthma using *Flovent* 100 mcg to >1500 mcg a day (Table 20). HPA axis suppression was typically related to dose of ICS, or ultimately plasma ICS level or total systemic bioavailability. Children receiving *Flovent* 200 - 400 mcg per day usually had normal or similar cortisol levels versus controls.

Table 20. *Flovent* (FP): HPA Axis Function with Provocative ACTH Stimulation or Insulin Tolerance Test

Design, Treatment	Patients, Treatment History	ACTH Stimulation
[46]6 months, NB, R, PG. Months 1-2: FP 250 powder or BUD powder 400 mcg BID; Months 3-6 FP 100 or BUD 200 mcg, BID, C: CRO, NED	N = 75, 6 -15 years old, no ICS or systemic steroids prior year, 83% newly diagnosed with asthma	At month 2: 23% had abnormal cortisol after FP 250 & BUD 400. Month 4: abnormal tests in BUD 200 vs. FP 100 group (9 vs. 5; P <0.05). Month 6: cortisol lower with BUD 200 vs. C (P <0.01), & similar between FP 100 vs. C
[47] 12-week, DB, R, CO, no washout, FP 750 or BDP 1500 mcg, both BID MDI, spacer	N = 30, 5-15 years old, BUD/BDP 1-2 mg/day, some systemic steroids	24-hour UFC: no significant differences between FP & BDP. Abnormal results occurred in 18 & 19 patients on FP & BDP, respectively
[48] 24-week, NB, controlled. FP 200 mcg BID (adjusted for symptoms, mean 360 mcg/ m^2/day) MDI, spacer	N = 20, 2.5-5 years old, no ICS	All patients had a normal peak cortisol conc. ≥20 mcg/dL. No significant difference in mean fasting AM cortisol conc. for FP vs. C
[49] 4-week, hCRH stim. test. FP 100-200 mcg or BUD 800 mcg/day	N = 14, 7-16 years old, ICS use not reported	Plasma cortisol: no effect from either treatment, and no significant difference between FP & BUD
[50] 5-16 weeks, open-label, insulin tolerance test (ITT). FP 250-750 mcg/day via Volumatic spacer	N = 18, 7-17 years old, no other ICS or systemic steroids	60 min serum cortisol: 9/18 had adrenal suppression (≤ 500 nmol/L). 6/9 dose-related suppression on FP >500 mcg/m^2/day; FP stopped. After 2-3 months, ITT was repeated with no suppression
[51] Cross-section, low dose Synacthen 500 ng/1.73 m^2 IV	N = 192, 2.6-19 years old, receiving FP ≥500 mcg/day, median 4 years	Normal peak cortisol (>500 nmol/L): 104 (54%). Impaired (≤500 nmol/L): 82 (43%); 1 patient was symptomatic. Flat (≤500 nmol/L with increment & basal AM cortisol <200 nmol/L); 6 (3%), all asymptomatic
R = randomized, DB = double-blind, CO = crossover, NB = non-blinded, BUD = budesonide, CRO = cromolyn, NED = nedocromil, BDP = beclomethasone dipropionate, hCRH = human corticotrophin releasing hormone, UFC = urinary free cortisol, C = control, PG = parallel-group, BID = twice daily		

Most children receiving *Flovent* ≤ 400 mcg per day had 12- or 24-hour overnight urinary free cortisol (UFC) and AM plasma cortisol concentrations that were within normal limits in studies lasting 6 weeks to 2 years (Table 21). One study measuring 12-hour overnight UFC found that children receiving *Flovent* inhalation powder plus FP intranasal formulation 100 mcg daily had normal cortisol values.

Table 21. *Flovent* (FP): HPA Axis Function Determined by Urinary and AM Plasma Cortisol Tests

Design, Treatment	Patients, Treatment History	Results
[33]6-week, CO. Weeks 1-2: placebo; Weeks 3-6: FP HFA MDI 88 mcg BID	N = 40, 4-11 years old with asthma, FP HFA 88 mcg BID	24-hr urinary cortisol: FP HFA similar vs. PL. Odds ratio: 0.987 (95% CI 0.796-1.223)
[52] 8-week, R, DB. Week 1-4: FP powder 100 mcg/day; Weeks 5-8 add FP IN 100 mcg/day or PL	N = 27, asthma & allergic rhinitis, 4-12 years old, FP 88-100 mcg/day	12-hr overnight UFC: normal for IN + inhaled FP group. UFC/Cr at baseline & week 4 were similar for FP vs. PL (*P* = 0.96 & 0.91, respectively).
[53] 6-week period, DB, R, CO, no washout. BDP (same dose), FP (1/2 BDP dose), MDI, spacer	N = 34, 5-13 years old, BDP/BUD 400-909 mcg/m^2/d, no oral steroids prior 3 months	24-hr UFC & metabolites: similar between FP vs. BDP groups. FP group had higher metabolite conc. (*P* = 0.04) & total UFC/Cr metabolites (*P* = 0.14) vs. BDP group.
[54] 2-year, FP 176-1320 mcg/day, MDI, spacer; if abnormal, then lower & retest after 3 months. No baseline report	N = 62, mean 11.6 years old, mod-severe asthma, 84% using ICS for mean 25.7 months	AM cortisol after month 8: low abnormal in 17% & 43% on FP 176 & ≥880 mcg/day, respectively. 17/22 patients changed to a lower dose of FP or other ICS; after 3 months, normal in 13/17, & cortisol significantly increased in FP 176 & ≥880 mcg groups overall
[55] 24 months, R, DB. FP 200 mcg daily, or FP 1 mg/day, stepped-down every 2 months to 500, 200, 100 mcg/day	N = 55, 6-10 years old, mild-mod asthma, prior ICS therapy	24-hour UFC metabolite excretion was significantly lower for FP 1000 & 500 mcg/day vs. FP 200 mcg/day. No other significant differences between groups.
[56] 12-month, R, PG, NB study, FP 100 mcg BID or SCG 5 mg QID, both MDI, spacer	N = 625, 1-3 years old, recurrent wheeze, 61%-65% steroid-naive	FP: mean AM serum cortisol 10% lower at 1 year (*P* = 0.05 vs. SCG), but was within normal range. 12-hour UFC/Cr was lower by 14% (*P* = 0.008 vs. SCG), but no patient had measurement below lower limit at week 28 & 52.
[57] R, DB, CO, two 3-week periods. Mean FP 222 mcg & TAA 1010 mcg daily	N = 21, 6-16 years old, mild-mod asthma, mean BDP equivalent 392 mcg/day, no systemic steroid prior 6 weeks	24-hour UFC/Cr: no difference from baseline vs. TAA or FP; or TAA vs. FP. UFC/BSA: FP similar vs. baseline (20.9 vs. 20.6, respectively) and higher vs. TAA (*P* = 0.035).
[58]Three 15-18 day periods, R, DB, PL-C, 2-week washout; 1) FP or BUD powder 200 mcg/day; 2) FP or BUD powder 400 mcg/day	1) N = 24; 2) N = 24; 6-12 years old, mild asthma, no steroids last 2 months	24-hour UFC/Cr: FP 200 lower vs. PL (*P* = 0.006) & similar vs. BUD 200 (*P* = 0.07); BUD 200 similar vs. PL (*P* = 0.32). FP 400 was lower vs. PL (*P* ≤0.001) & similar vs. BUD 400 (*P* = 0.29); BUD 400 lower vs. PL (*P* = 0.0001).

R = randomized, DB = double-blind, CO = crossover, PL-C = placebo-controlled, BUD = budesonide, BDP = beclomethasone dipropionate, PL = placebo, UFC/Cr = urinary free cortisol, creatinine corrected, MDI = metered dose inhaler, IN = intranasal, SCG = sodium cromoglycate, QID = four times daily, BSA = body surface area, TAA = triamcinolone, PG = parallel-group, NB = non-blinded, BID = twice daily

Table 22. Effect of *Flovent* (FP) on HPA Axis in Infants

Design	Patients Treatment	Results
[59] 14-day, DB, R, PL-C, pilot study, corticotropin-releasing hormone test. FP 500 mcg BID MDI	25 premature infants (mean gestational age of 26 weeks), ≤24 hours old, on mechanical ventilation	Basal & post-stim. (15, 30, 60 min): plasma ACTH & serum cortisol conc. were significantly suppressed in the FP vs. PL group.
MDI = metered dose inhaler, BID = twice daily, PL-C = placebo-controlled, DB = double-blind, R = randomized, PL = placebo		

6.3 Studies Assessing the Effects on Growth in Children

CLINICAL STUDIES ON GROWTH

The benefits of corticosteroid therapy for asthma should be weighed against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

Data from studies using *Flovent* HFA, *Flovent Diskus*, *Flovent* powder (*Rotadisk* via *Diskhaler*), and *Flovent* MDI (CFC, chlorofluorocarbon propellant) are presented.

Growth remained in the normal range in children receiving *Flovent* CFC or powder 200 mcg daily in long-term trials of 1 year or longer (Table 23).

Table 23. *Flovent* (FP) in Children in Long-Term Growth Studies

Design	Patients	Treatment	Results
52-week, DB, R, PG, PL-C, growth study. Stadiometry monthly. Radiographic bone age (left hand & wrist) weeks 0, 24, 52. [60] [61]	325 prepubescent males 4-11 years old & females 4-9 years old, normal growth prior 6-18 months, used systemic steroids ≤ 60 total days in prior 2 years. Prepubescent growth analysis dropped children reaching puberty during trial.	FP powder 50 mcg BID (n = 98), FP powder 100 mcg BID*(Rotadisk)* (n=89), or PL (n=76)	Mean ITT growth velocity was 6.32, 6.07, & 5.66 cm/year in the PL, FP 50 & FP 100 groups, respectively. A subset who remained prepubertal had growth rates of 6.10 cm/year in the PL group (n = 57), 5.91 cm/year in the FP 50 group (n = 74), and 5.67 cm/year in the FP 100 group (n = 79)*. The % children entering puberty were not evenly distributed among groups. A higher dropout rate occurred in the poorly-controlled asthma PL group.
*The expected growth velocity range (3rd, 50th, 97th percentile) in boys 8.5 years old is 3.8, 5.4 , & 7.0 cm/year, respectively; for girls (3rd, 50th, 97th percentile), the velocity is 4.2 , 5.7 , & 7.3 cm/year, respectively. SDS: standard deviation score, ITT: intent-to-treat population, R = randomized, DB = double-blind, BID = twice daily, PG = parallel group, PL-C = placebo-controlled			

Design	Patients	Treatment	Results
1-year growth study(62)	41 children 6-12 years old with moderate to severe asthma	FP powder 50 & 100 mcg *(Rotadisk)* BID	Growth was similar in the FP group vs. national standards. There was no significant difference in height velocity in the 30 children with pre- and post-FP treatment measurements.
1-year, open label, R, growth study(63)	100 children, moderate persistent asthma, 4-11.5 years old, symptomatic on albuterol	FP CFC 125 mcg with spacer or BUD 200 via Turbuhaler, both BID	There was no difference between groups in growth velocity
*The expected growth velocity range (3rd, 50th, 97th percentile) in boys 8.5 years old is 3.8, 5.4 , & 7.0 cm/year, respectively; for girls (3rd, 50th, 97th percentile), the velocity is 4.2 , 5.7 , & 7.3 cm/year, respectively. SDS: standard deviation score, ITT: intent-to-treat population, R = randomized, DB = double-blind, BID = twice daily, PG = parallel group, PL-C = placebo-controlled			

SHORT-TERM GROWTH STUDIES

Patients receiving *Flovent* 200 mcg daily had similar growth measurements compared with controls in several studies (Table 24). One study reported patients receiving *Flovent* 400 mcg daily had reduced rates of growth compared with placebo, but had similar growth rates compared with patients receiving budesonide 400 or 800 mcg daily.

Table 24. *Flovent* (FP) CFC and *Diskus* in Short-Term Studies < 1 Year Long

Design	Patients	Treatment	Results
6-week, open-label, non-randomized growth trial, 2-week washout; Knemometry performed every 2 weeks. (64)	21 prepubescent children 6-10 years old, asthma, mean $FEV_1$102% -103% predicted	FP powder 100 mcg *(Rotadisk)* BID *via Diskhaler*, then washout	Lower leg growth velocity during treatment with FP was not significantly different from that during the washout period.
R, DB, CO growth trial, 3 treatment periods & 2 PL washouts, all 2 weeks each (65)	19 children, 7-14 years old, mild asthma.	FP powder*(Rotadisk)* 200 mcg daily; BDP powder 400 or 800 mcg daily, all *Diskhaler device*	Treatment with both doses of BDP resulted in a significant reduction in growth velocity vs. FP. Mean growth velocities during treatment with FP 200, BDP 400, and BDP 800 were 0.34, 0.09, and 0.06 mm/week, respectively. The mean lower leg growth velocity during the 2nd washout periods was 0.61 and 0.80 mm/week.
SDS: standard deviation score; BIA = bioelectrical impedance analysis, DEXA = dual energy X-ray absorptiometry, R = randomized, DB = double-blind, DD = double-dummy, PL-C = placebo-controlled, PG = parallel group, CO = crossover, BID = twice daily, MDI = metered dose inhaler, PL = placebo, BUD: budesonide, CFC: chlorofluorocarbon propellant			

Design	Patients	Treatment	Results
20-week, R, DB, DD, PG, 20-week follow-up (66)	333 prepubescent children, 4-12 years old, mod.-severe asthma, receiving BDP 400-800 mcg or FP 200-400 mcg daily	FP powder 400 mcg daily via *Diskus;* BUD powder 800 mcg daily via Turbuhaler	The linear growth velocity in the BUD group was less vs. FP group: mean difference 6.2 mm (P = 0.0003). The difference in adjusted mean height increase was 13.2 mm (P = 0.0024) in favor of FP in a subgroup of 154 patients; FP (n = 76), BUD (n = 78) with stadiometry measurements.
Three 2-week periods each separated by 2-week washouts, DB, PL-C, DD, CO, growth study, knemometry 2x/week (58)	48 children, 6-12 years old, mild asthma	FP powder 200 or 400 mcg daily (n = 24 each); BUD powder 200 or 400 mcg daily (n=24 each); PL	FP 200 (0.38 mm/week) & BUD 200 (0.26 mm/week) had similar growth rates vs. PL (0.35 mm/week). In the 400 mcg groups, growth rates were reduced: FP 400 (0.37 mm/week) & BUD 400 (0.30 mm/week) vs. PL (0.52 mm/week); difference was only significant for BUD 400 vs. PL. There was no significant difference between growth rates in low or high-dose FP vs. low or high-dose BUD groups.
6-month growth & body composition study, anthropometry, BIA & DEXA (67)	26 children, 3.9 to 14.9 years old, asthma not controlled with sodium cromoglycate and prn albuterol, no oral steroids prior 6 months	FP CFC 100 mcg BID; BUD powder 200 mcg BID; Control	No statistically significant differences in change of growth velocity (adjusted for pubertal status) and weight were observed among groups. SDS below 50th percentile was 35%, 45%, and 44%, and below 3rd percentile was 18%, 22%, & 12.5% of FP, BUD & control groups, respectively.

SDS: standard deviation score; BIA = bioelectrical impedance analysis, DEXA = dual energy X-ray absorptiometry, R = randomized, DB = double-blind, DD = double-dummy, PL-C = placebo-controlled, PG = parallel group, CO = crossover, BID = twice daily, MDI = metered dose inhaler, PL = placebo, BUD: budesonide, CFC: chlorofluorocarbon propellant

6.4 Studies Assessing the Effects on Bone Metabolism and Mineral Density in Children with Asthma

LONG TERM STUDIES (≥1 YEAR)

Dose-Dependent Effect of *Flovent*

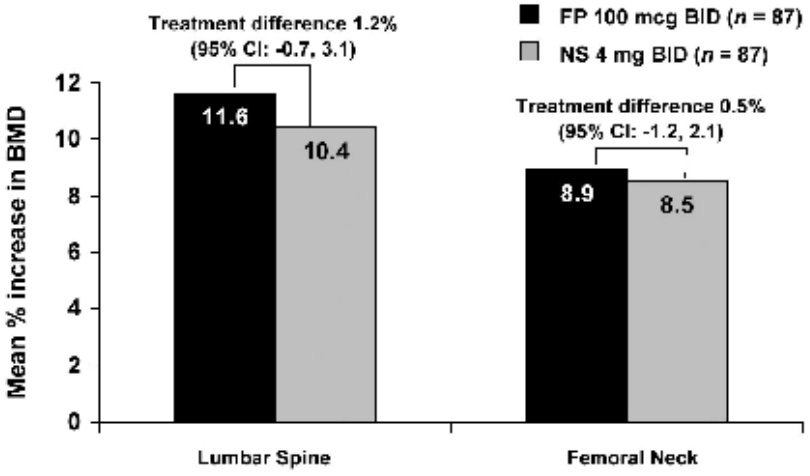
A 2-year, randomized, double-blind study in 55 children with asthma evaluated the dose-dependent effects of *Flovent* on bone metabolism. (55) Children were 6-10 years of age with mild-to-moderate persistent asthma and previously receiving inhaled corticosteroids. Children were randomized to receive either *Flovent* inhalation powder 200 mcg/day at a constant dose for 2 years (n = 27) or a high starting dose of *Flovent* 1000 mcg/day for 6 months followed by reductions every 2 months to 500, 200 and 100 mcg/day (n = 28) during the remaining 18 months. Markers of bone metabolism and BMD were similar at baseline. Serum osteocalcin, serum P1NP, and urinary deoxypyridinoline decreased significantly during treatment with *Flovent* 1000 and 500 mcg/day compared with 200 mcg/day. Similar serum osteocalcin levels were observed when both groups received 200 mcg/day (constant) or 200 mcg/day and 100 mcg/day. Urinary deoxypyridinoline and serum P1NP were significantly higher among step-down patients receiving 100 mcg/day at month 18 compared with patients receiving a constant dose of 200 mcg/day. No significant

differences between groups were seen in BMD after 2 years. It was concluded that dose-dependent biochemical bone turnover was found with *Flovent* 1000 and 500 mcg/day compared with 200 mcg/day.

***Flovent Diskus* (FP) 200-400 mcg/day versus Nedocromil Sodium (NS)**

Roux et al [68] conducted a 24-month, randomized, open-label, parallel-group study in 174 children 6-14 years of age with mild-to-moderate persistent asthma comparing the effect of *Flovent Diskus* 200-400 mcg/day (n = 87) and NS 8-16 mg/day (n = 87) on BMD. DEXA measurements of lumbar spine and femoral neck were recorded at baseline, 6, 12 and 24 months. At month 24, the adjusted mean percentage increase in lumbar spine BMD and femoral neck BMD were similar between groups (Figure 6).

Figure 6. Increase in Bone Mineral Density after 24 months with FP or Nedocromil Sodium



Fluticasone Propionate 200 mcg/day versus Beclomethasone Dipropionate (BDP) 400 mcg/day

Gregson et al [69] conducted a double-blind, randomized, parallel-group study in 23 steroid-naïve, prepubescent children (15 boys, 8 girls) aged 5-10 years old with moderately severe asthma to investigate the effects of *Flovent* and BDP on BMD. Children were randomized to *Flovent* 100 mcg twice daily or BDP 200 mcg twice daily for 20 months (inhalation devices not reported). DEXA scans were performed regularly. Densitometry of lumbar spine and total body showed a significant increase over time that followed the normal increases in density with age. There was no difference between the two treatment groups for BMD, with no change in fat distribution or increase in the percentage of total body fat.

SHORT-TERM STUDIES

Fluticasone propionate (FP) versus budesonide (BUD)

Kannisto et al evaluated the changes in biochemical markers of bone metabolism in relation to adrenal function and growth during the initiation phase of inhaled corticosteroid therapy in 75 children 6-15 years old with newly diagnosed asthma. [70] Patients were randomized to open-label treatment with BUD inhalation powder 800 mcg/day for 2 months followed by 400 mcg/day for 2 months (n = 30), *Flovent* (inhalation powder) 500 mcg/day for 2 months followed by 200 mcg/day for 2 months (n = 30), or sodium cromoglycate 20-60 mg/day or nedocromil 12 mg/day for 4 months (n = 15). The groups were similar in all baseline measurements, except for serum P1CP being higher in the BUD group than in those receiving *Flovent* or cromolyn (P<0.05). The patients in the cromolyn group had slight increases in serum OC, P1CP, and ICTP over the 4 months, with a normal low-dose adrenocorticotropic hormone (ACTH) test. In those receiving *Flovent*, ICTP and OC decreased after the first 2 months, but returned to pretreatment level at month 4. Treatment with*Flovent* resulted in a slight increase in P1CP over the 4 months. In the BUD group, a significant decrease in OC and P1CP occurred at month 4; however, ICTP did not significantly change. Children who developed growth or adrenocortical suppression were more

likely to have changes in bone metabolism. It was concluded that both inhaled BUD and *Flovent* caused dose-dependent effects on biochemical markers of bone metabolism.

Effects of High Dose Fluticasone Propionate

Griffiths et al [71]conducted a cross-sectional study evaluating the effects of high dose *Flovent* on bone density and biochemical markers of bone metabolism in children with moderate to severe asthma. Children 5 to 19 years of age (n = 49) who had been receiving *Flovent* 1000 mcg daily for at least 6 months and 32 healthy controls (age and gender-matched) were entered into the study. The dose of *Flovent* (chlorofluorocarbon MDI with spacer or inhalation powder via *Diskus*®) was judged by the treating physician to be the minimum effective dose to maintain asthma control in each case. No child had taken oral corticosteroids within the previous month. To minimize diurnal variability, sample times were standardized to 8-10 AM and second morning void for fasting spot urine.

There was no significant difference in baseline data between cases and controls for age, bone age, height, weight, and body mass index (absolute BMI, $P = 0.03$; after conversion to z-score, $P = 0.08$). All children were concurrently on long-acting $beta_2$-agonists. The mean dose of *Flovent* was 771.2 mcg/m^2/day (range 476 to 1429 mcg), and mean duration of *Flovent* therapy was 2.86 years (range 0.5 to 6.0). The duration of time since last dose of oral prednisolone was a mean of 13.2 months (range 1 month to 12 years). Other pertinent medications included calcium supplements, oral contraceptives, hydrocortisone for adrenal insufficiency, and corticosteroid nasal spray. There was no significant difference between cases and controls in measures of bone synthesis: serum osteocalcin, P1NP, ALP, and BALP or measures of bone resorption: urine deoxypyridinoline, a bone collagen crosslink/Cr ratio and NTx/Cr ratio.

The cases and controls spanned Tanner stages I-V, but there was no significant difference in their distributions. Analysis of bone age and chronological age was conducted since bone density would be dependent on the timing of puberty. DEXA total body z-scores for chronological age of -1.0 were recorded for 7.9% of cases (3/38); after correction for bone age, 5.4% of cases (2/37) remained in this range. DEXA lumbar spine z-scores for chronological age less than -1.0 were recorded in 35.1% of cases (13/37); correction for bone age left 16.2% of cases (6/37) in this range. After bone age correction, there was no significant difference between z-scores of the cases and a reference population.

Effects on Bone Metabolism in Infants

Teper et al [72]evaluated 2 doses of *Flovent* for effects on clinical outcome, growth, bone metabolism and serum cortisol in 30 infants 6 to 24 months of age with asthmatic symptoms (≥3 episodes of wheeze and clinical improvement after bronchodilator), and a familial history of atopy in first-degree relatives. The inhaled steroid-naïve patients were randomized to placebo, *Flovent* 100 mcg or 250 mcg per day (CFC MDI with holding chamber attached to a face mask) in a 6-month, double-blind, placebo-controlled study. No significant differences in baseline data among the groups were found. Treatment in the *Flovent* 100 and 250 groups did not have a significant effect on linear growth, serum insulin-like growth factor-binding protein 3, serum osteocalcin, serum bone alkaline phosphatase fraction, and serum cortisol.

6.5 Studies Assessing the Effects on Bone Metabolism/Osteoporosis in Adults with Asthma

TWO-YEAR STUDIES

***Flovent* (chlorofluorocarbon or CFC) Inhalation Aerosol 88 or 440 mcg BID vs. Placebo**

A two-year, randomized, double-blind, parallel group trial compared the effects of FP CFC 88 mcg (n = 55) or 440 mcg (n = 51) twice daily with placebo (n = 54) on bone in adults with mild asthma and minimal pre-study exposure to corticosteroids. [73] Bone mineral density was analyzed by DEXA measurements of the lumbar spine, proximal femur and total body every six months and compared with baseline. Additionally, serum osteocalcin was measured every six months. At week 104, mean BMD at

the 3 skeletal sites did not differ among groups ($P > 0.20$). The mean percent change from baseline in lumbar spine was similar: + 0.21 (placebo), +0.68 (FP 88 mcg), and –0.28 (FP 440 mcg). Mean serum osteocalcin values declined slightly in all groups: -5.5 (placebo), -4.1 (FP 88 mcg), and -5.9 ng/mL (FP 440 mcg) ($P > 0.20$). There were no skeletal fractures in any group.

Flovent powder 500 mcg twice daily vs. Placebo

A two-year study assessed the effects of *Flovent* ®*Rotadisk*® 500 mcg twice daily via *Diskhaler*® (n = 32) on the skeletal bones of 64 adult with mild persistent asthma (males 18-50 years old; pre-menopausal females 18-40 years old).[74] This study had a randomized, double-blind, parallel-group, placebo-controlled (n = 32), prospective design. BMD of the lumbar spine was performed by DEXA. Serum osteocalcin and urine N-telopeptide were evaluated at screening and every six months.

No significant differences for BMD or biochemical bone markers were detected between groups. Two patients in the placebo group and three in the FP group showed ≥ 5% decrease in BMD from baseline; however, only one patient (FP group) was withdrawn per pre-determined protocol after repeat scans.

Flovent CFC 500 mcg BID vs. Beclomethasone Dipropionate CFC 1000 mcg BID

Egan et al [75] compared the effects of FP CFC 500 mcg twice daily and BDP CFC 1000 mcg twice daily on BMD and bone metabolism in a two-year, randomized, double-blind, parallel-group study. Medication was administered using a large volume spacer. Thirty-three adults with asthma with expected stable peak bone mass (males 18-50 years old; pre-menopausal females 18-40 years old) participated in the study. Corticosteroid history included 1000-2000 mcg/day of inhaled BDP or budesonide and up to two courses of oral steroids in the last year; however, no patients had received oral corticosteroids in the last two months. Bone therapies such as hormone replacement, calcitonin, and bisphosphonates were not permitted. Three open-label control groups were included: 1) mild asthma receiving ≤ 400 mcg/day BDP or budesonide (n = 16); 2) chronic, severe asthma receiving ≥ 10 mg/day of oral prednisolone and mean 1500 mcg/day ICS (n = 8) ; and 3) healthy volunteers (n = 7).

BMD was measured at 0, 6, 12, and 24 months using QCT of vertebral trabecular spine (both single and dual energy low-dose scanning techniques), single-photon absorptiometry (SPA) of forearm, and DEXA of lumbar spine, femoral neck, and whole body. Markers of bone formation (serum osteocalcin, bone alkaline phosphatase, procollagen type I C-terminal propeptide) and bone resorption (urine C-telopeptide of type I collagen and free deoxypyridinoline relative to creatinine) were measured every three months.

Overall, 24/33 patients completed the two-year study. Prior oral corticosteroid exposure was comparable in the treatment groups. The reasons for attrition included noncompliance and social reasons in two patients (FP) and low serum cortisol, noncompliance, and asthma exacerbation in 7 patients (BDP). At baseline, BMD was lower in patients who had received both low and high dose ICS compared with BMD in healthy volunteers (Table 25). Mean vertebral trabecular spine BMD (single energy QCT) remained stable in patients who received FP and declined in patients treated with BDP. Similar results were observed with dual energy QCT, suggesting that the changes observed were due to changes in bone mineral and not due to changes in marrow fat. No significant changes in measures of SPA and DEXA or markers of bone metabolism were observed.

Table 25. Single Energy QCT Analysis of Vertebral Trabecular Spine BMD

Month	Mean (SD), mg/cm^3					
				Open-Label Control Groups		
	FP 1000 mcg/day	BDP 2000 mcg/day	Difference FP vs. BDP	Low dose ICS, n = 16	Prednisolone + High dose ICS, n = 8	Healthy volunteers, n = 7
0	152 (28)	152 (16)	----	152 (21.2)	99 (24.2)	169 (18.2)
12	154 (29.2)	144 (19.5)	9*	144 (23.2)	91 (24.6)	164 (17.6)
24	153 (26.8)	145 (19.6)	9*†	143 (25.2)	91 (22.1)	162 (18.2)
*Adjusted mean difference, $P = 0.0006$; †$P = 0.004$						

ONE-YEAR STUDIES

***Flovent* CFC (chlorofluorocarbon) 200 mcg and 375 mcg twice daily or BDP CFC 400 mcg and 750 mcg twice daily**

Medici et al [76] conducted a one-year, double-blind, parallel-group trial evaluating the effects of treatment with low and high doses of inhaled *Flovent* and BDP on BMD and biochemical markers of bone metabolism in adults with mild-to-moderate severe asthma. After a 4-week run in period to standardize their regular ICS therapy to either BDP 400 mcg or 750 mcg BID, patients were randomized to either low dose *Flovent* 200 mcg twice daily (n = 22) or BDP 400 mcg twice daily (n = 21) or high dose *Flovent* 375 mcg twice daily (n = 13) or BDP 750 mcg twice daily (n = 13). Medications were administered with a large volume spacer device. Markers of bone formation and resorption were measured at baseline, 6, and 12 months. BMD of the radius and tibia was measured using peripheral QCT and DEXA, and DEXA was used to measure the lumbar spine. The primary safety endpoint was BMD of the distal radius as measured by pQCT.

Overall, there was no clinically significant loss of bone in the distal radius or tibia in any patient. There was also no significant change from baseline in bone density of lumbar spine at 6 or 12 months between patients receiving high-dose *Flovent* or BDP; however, there was a negative change from baseline in the low-dose patients taking BDP compared to the *Flovent* group at 12 months ($P = 0.02$). No consistent pattern of changes from baseline in bone markers were observed during the study.

Flovent CFC 250 mcg, 375 mcg, 500 mcg vs. BDP CFC 500 mcg, 750 mcg, 1000 mcg twice daily

A double-blind, 6-month period crossover study compared the safety of *Flovent* and BDP in 306 patients 18-75 years old with moderate to severe asthma.[77] All patients were receiving regular treatment with BDP or budesonide 800-2,000 mcg daily. During a one month run-in, all bronchodilator medication (except theophylline) was changed to salmeterol powder 50 mcg twice daily via *Diskhaler*. Patients were then randomized to *Flovent* 250 mcg, 375 mcg, 500 mcg twice daily or BDP 500 mcg, 750 mcg, 1000 mcg twice daily based on their previous ICS requirements. BMD of the lumbar spine and the hip was measured using DEXA. BMD was only measured during the first treatment period and analyzed as a parallel-group design.

After 6 months, patients receiving *Flovent* (n = 105) had significantly increased BMD in the lumbar spine (1%) and femoral ward's triangle (2.9%) compared to baseline ($P < 0.01$) and compared to BDP (n = 102; $P = 0.05$). BMD of the femoral neck was not changed in the *Flovent* group and was significantly lower in those receiving BDP ($P < 0.01$). After 1 and 6 months of treatment, neither *Flovent* nor BDP groups had a significant change of morning serum cortisol or markers of bone metabolism (urinary calcium/creatinine or hydroxyproline/creatinine). Serum osteocalcin levels were significantly higher after 1 month ($P = 0.041$) and 6 months ($P < 0.001$) after *Flovent* vs. BDP treatment.

During a 2-year, open-label extension,[78] patients were maintained on *Flovent* 440 to 800 mcg/day MDI. Overall, 142 patients completed the study. DEXA measurements were performed every 6 months. No decrease in BMD in any site was observed. There was a significant increase in BMD of the lumbar spine in both males (mean increase 1.27%) and females (mean increase 0.96%) and a significant increase in BMD of trochanter in males (mean increase 2.4%). No significant effect on biochemical measures was observed.

Flovent CFC 500 mcg twice daily vs. Budesonide CFC 800 mcg twice daily with spacers

The effects of *Flovent* and budesonide on bone markers and BMD were evaluated in a randomized, prospective, open-label, parallel-group study in 59 patients with asthma.[79] Patients, previously stabilized on BDP 1500-2000 mcg daily or budesonide 1200-1600 mcg daily, were randomized to *Flovent* CFC 500 mcg twice daily or budesonide CFC 800 mcg twice daily both delivered via large volume spacers.

Markers of bone turnover {osteocalcin, PICP, immunoreactive free deoxypyridinoline (iFDpd), and N-terminal crosslinked telopeptides of type I collage (NTx)}, as well as serum and urinary cortisol concentrations were measured at baseline, 6, and 12 months. BMD was measured at the spine and proximal femur (neck and trochanter).

Despite randomization of patients, subjects receiving *Flovent* were more likely to be women, younger, and to have more severe asthma as indicated by past oral corticosteroid use and baseline lung function. No differences were noted in spinal BMD in patients regardless of a history of use of oral steroids. Increase in spinal BMD was not significantly different between *Flovent* (0.49%) and budesonide (1.59%) after 1 year ($P = 0.36$). The change of BMD of the femoral neck (adjusted for oral steroids during study) and trochanter were similar between groups ($P = 0.31$).

Osteocalcin significantly increased from baseline in both treatment groups with no differences between groups. PICP levels did not differ between groups. Neither osteocalcin nor PICP was affected by the use of oral steroids during the study. Markers of bone resorption, iFDpd and NTx, varied considerably during the study. Patients receiving *Flovent* had a 1.3% decrease in iFDpd compared with an 8.2% increase in the budesonide group ($P = 0.48$). NTx decreased slightly for both *Flovent* (0.39%) and budesonide (1.6%) groups ($P = 0.9$). Overall, bone resorption markers were dependent on oral steroid use during the study. Urinary free cortisol levels were 56.4 nmol/L and 44.0 nmol/L representing a decrease of 14.8% and 6.2% in patients receiving *Flovent* and budesonide, respectively; no significant difference was noted between groups. Serum cortisol levels increased slightly during the 12 months with no difference between treatments.

COHORT STUDIES

A retrospective cohort study was conducted using a large UK primary care database to compare the fracture risks of patients receiving ICS (n = 170,818) to patients with obstructive airway disease or asthma using bronchodilators alone (n = 108,786) and control subjects (n = 170,818). [80] Control patients were matched by age, gender, and medical practice and had not received ICS or systemic corticosteroid prescriptions. Patients who had received at least two prescriptions were included in the analysis. Three dose categories were identified: low dose (< 300 mcg/day), medium dose (300-700 mcg/day), and high dose (≥ 700 mcg/day). Overall, BDP was the most frequently prescribed ICS (87%) followed by budesonide (11%) and FP (2%).

After adjustment for potential confounding variables (coexisting disease, concomitant drug therapy, and a baseline history of fracture or back pain), the rate of non-vertebral fractures was significantly elevated among ICS users compared with control patients (RR = 1.15, 95% CI: 1.10, 1.20). No difference in non-vertebral fracture risk was observed between the ICS and bronchodilator groups (RR = 1.00; 95% CI: 0.94, 1.06). The rate of non-vertebral fractures among users of budesonide and FP was similar to that of BDP. The relative rates of hip and vertebral fractures were also higher during ICS therapy compared with that of controls (1.22 and 1.51, respectively).

In addition, a dose response was found for hip and vertebral fractures in patients who received ICS compared to controls. Hip fracture risk was 0.95 with BDP < 300 mcg/day and increased to 1.77 at

doses of ≥ 700 mcg/day. Vertebral fracture showed a similar dose-related risk with the highest risk in the high-dose ICS group compared with controls (RR = 2.50). No consistent trend in the rate of fractures for ICS compared to bronchodilators was observed.

Elmstahl et al[81] recruited patients from a Swedish population-based prospective cohort study on diet and health outcomes and evaluated the effects of ICS on BMD. The study included 155 postmenopausal women treated with ICS (budesonide, n = 136; BDP, n = 13; FP, n = 6) and 674 unexposed control subjects. In the group of 155 women, only 106 were exposed to ICS alone; however, the other 49 women also had exposure to either oral corticosteroids (OCS) for > 1 month, intra-articular steroid injections, or both in addition to ICS. BMD via X-ray absorptiometry of the nondominant forearm was measured. A questionnaire concerning corticosteroid use including oral, inhaled, nasal, intra-articular and dermal application and medical history was completed. The ICS study population had a mean duration of ICS usage of 8.2 ± 5.03 years, mean ICS daily dose of 853 mcg, and 23% had a daily dosage > 1000 mcg.

Mean BMD values did not differ significantly between groups: 0.426 and 0.429 g/cm^2 for ICS-exposed (n = 155) and control subjects, respectively. Similar BMD values (0.427 and 0.426 g/cm^2) were measured in women using ICS < 6.3 years versus women who used ICS ≥ 6.3 years, respectively. No association was found between age-adjusted BMD and annual duration of ICS exposure among the 155 women or among those only exposed to ICS (n = 106). In addition, the study did find a non-significant but numerically lower BMD for women who received an ICS daily dose ≥ 1000 mcg (0.410 ± 0.077 g/cm^2) versus those who received < 1000 mcg of ICS (0.439 ± 0.070 g/cm^2).

7. COMPARATIVE DATA

7.1 Comparison with Montelukast in Children with Asthma

CLINICAL INFORMATION

Flovent Diskus Compared with Montelukast

A 12-week, randomized, double-blind, parallel group, double-dummy study compared *Flovent Diskus* 50 mcg twice daily with montelukast 5 mg daily in children 6-12 years old with persistent asthma receiving only short-acting beta$_2$-agonists. [82] Patients (N = 342) had an FEV_1 60%-85% of predicted with a ≥12% increase in FEV_1 within 30 minutes following albuterol administration. The primary endpoint was percent change from baseline in morning pre-dose FEV_1 at endpoint. Children receiving *Flovent Diskus* had a significantly greater improvement in the primary endpoint as well as most of the secondary measures (Table 26).

Table 26. *Flovent Diskus:* Mean Change from Baseline at Endpoint

	***Flovent Diskus* 50 mcg BID (n = 168)**	**Montelukast 5 mg once daily (n = 167)**	**P-value**
Morning Pre-Dose FEV_1, %	10.6	4.6	0.002
AM PEF, L/min	39.9	23.0	0.004
PM PEF, L/min	35.5	20.4	0.02
Albuterol use, puffs/day	-1.43	-1.23	0.018
Rescue-free days, %	45.1	35.0	0.002
Symptom-free days, %	37.7	31.3	0.087
Daytime symptom score*	-0.81	-0.75	0.202
Nighttime symptom score†	-0.40	-0.19	<0.001
Asthma exacerbations	19%	15%	0.401
*scale 0 to 5; †scale 0 to 3; table includes data from 335 patients. Data from 7 patients at 1 site excluded for study standards.			

The incidence of adverse events was similar between treatment groups. The most common adverse events in the *Flovent* and montelukast groups, respectively, were headache (13% vs. 12%), upper respiratory tract infection (12% vs. 11%), sore throat (10% vs. 12%), fever (10% vs. 7%), and cough (10% vs. 6%). Withdrawals due to drug-related adverse events occurred in two patients receiving *Flovent Diskus* (headache, nausea) and in one patient receiving montelukast (tingling tongue). In a small subset of patients (n = 29) who had both baseline and endpoint cortisol samples, the geometric mean of the 12-hour urinary cortisol ratio was not significantly different between *Flovent Diskus* and montelukast (0.9 vs. 0.75, respectively).

In a replicate study including 341 children, *Flovent Diskus* 50 mcg twice daily and montelukast 5 mg once daily both showed similar improvement in the primary endpoint, mean percent change from baseline in morning pre-dose FEV_1 (9.4% vs. 6.2%, respectively; $P = 0.138$). [83] Similar improvements between treatment groups were also observed for most secondary endpoints including PEF and daily albuterol use. However, patients treated with *Flovent Diskus* showed a significantly greater increase in the percent of symptom-free days compared with patients treated with montelukast (40.8% vs. 31.2%, respectively; $P = 0.031$).

The overall incidence of adverse events was similar between the two groups. The most common adverse events reported were headache and ear, nose and throat events. Asthma exacerbations occurred in 16% and 17% of patients receiving *Flovent Diskus* and montelukast, respectively. In patients who had evaluable cortisol samples at both baseline and endpoint (n = 88), the geometric mean of 12-hour urinary cortisol ratio was not significantly different between *Flovent Diskus* (1.35 mcg) and montelukast (1.14 mcg; $P = 0.837$).

Predictors of Response and Response Profiles

A randomized, double-blind, double-dummy, crossover study compared responses to treatment in children with asthma to identify patient characteristics that may be predictive of response with the treatment of *Flovent Diskus* and montelukast. [84] The study included children 6-17 years of age with mild to moderate persistent asthma ($FEV_1 \geq 70\%$ predicted) with asthma symptoms requiring a rescue bronchodilator more than 3 times per week. Patients (N = 144) were randomized to *Flovent Diskus* 100 mcg twice daily or montelukast 5-10 mg daily based on age for 8 weeks. Patients were then crossed over to the other arm. The first 4 weeks of each treatment period were considered a washout period and were not considered in the statistical analyses.

Results showed that the mean improvement in FEV_1 was 6.8% for *Flovent Diskus* and 1.9% for montelukast ($P < 0.001$) in 126/144 children who completed both periods. Based on the definition of 'response' (≥7.5% improvement in FEV_1), 17% of patients responded to both medications, 23% responded to *Flovent* alone, and 5% responded to montelukast alone. Patients who responded to *Flovent Diskus* alone versus responding to neither medication had higher baseline levels of exhaled nitric oxide, total eosinophil counts, serum IgE, eosinophil cationic protein with lower methacholine PC20 values and poorer pulmonary function. A favorable response to montelukast alone was associated with younger age (median 9 years) and shorter disease duration (4 years). Patients who responded to both medications had significantly higher urinary leukotriene E4 levels and lower pre-bronchodilator FEV_1 percent predicted and FEV_1/FVC values at baseline versus those responding to neither medication.

Response profiles were reported for 127/144 (88.2%) of children who completed both treatment arm measures. [85] Improvements in most clinical asthma control measures occurred with both treatments. However, clinical outcomes (asthma control days, Asthma Control Questionnaire, and albuterol use), pulmonary responses (FEV_1/FVC, PEF variability, morning PEF, and measures of impedance), and inflammatory biomarker (exhaled nitric oxide) improved significantly more in the group receiving *Flovent* versus those on montelukast treatment. Exhaled NO was both a predictor ($P = 0.011$) and a response indicator ($P = 0.003$) in asthma control day responses between *Flovent Diskus* and montelukast.

Decreased Anti-Inflammatory Activity Measured by Exhaled Nitric Oxide

A study was conducted to compare anti-inflammatory activity, as measured by fraction of exhaled nitric oxide (FeNO), relative efficacy and safety of low-dose *Flovent Diskus* and montelukast in children with mild to moderate persistent asthma. [86] Twenty-four children 5-12 years old on inhaled corticosteroids were switched to salmeterol for a 2-week run-in period, then randomized to treatment. Subjects received 4 weeks of therapy with placebo, montelukast 5 mg daily, or *Flovent Diskus* 50 mcg twice daily in a randomized, double-blind, double-dummy, three-way crossover fashion. FeNO and spirometry were measured at baseline and every 2 weeks.

Patients receiving treatment with *Flovent* had significantly lower FeNO after 2 and 4 weeks (10.78 and 11.0 ppb, respectively) compared with monteukast treatment (14.69 and 15.6 ppb, respectively) and placebo (13.1 and 13.9 ppb, respectively). FeNO after 4 weeks of montelukast (15.6 ppb) was significantly increased compared to baseline (11.7 ppb) and salmeterol run-in period (13.0 ppb), but was not different from placebo (13.9 ppb). Post-bronchodilator FEV_1 percent predicted was significantly higher following *Flovent* compared to placebo after 2 and 4 weeks, and was greater than montelukast treatment after 2 weeks. Evening asthma score was significantly lower after 2 weeks of *Flovent* compared to salmeterol, montelukast and placebo.

Use in Preschool Children with Wheezing, Cough and Shortness of Breath

The effect of *Flovent* versus montelukast on symptoms, lung function, and eosinophils in preschool children with asthma-like symptoms was compared with a double-blind, double-dummy study design. [87] Inclusion criteria were age 2-6 years, ≥4 out of 14 days with respiratory symptoms preceding the trial, and no recent use of steroids or montelukast. Data were collected at baseline and after 3 months. The primary study endpoint was symptom score (wheeze, cough and shortness of breath) recorded by caretakers. Secondary endpoints were lung function (interrupter technique, forced oscillation technique including frequency dependence) and blood eosinophils.

Patients randomized to montelukast (n = 18), *Flovent* (n = 25), and placebo (n = 20) were a mean 3.8 ± 1.4 to 3.9 ± 1.1 years old. The asthma symptom scores improved more for those receiving *Flovent* versus placebo. Patients receiving *Flovent* had less frequency dependence at follow-up versus the montelukast group ($P = 0.048$). Blood eosinophils decreased more in the montelukast group compared with placebo ($P = 0.045$).

7.2 Comparison with Montelukast in Patients 12 Years of Age and Older with Asthma

CLINICAL INFORMATION

Effect on Lung Function and Asthma Symptoms

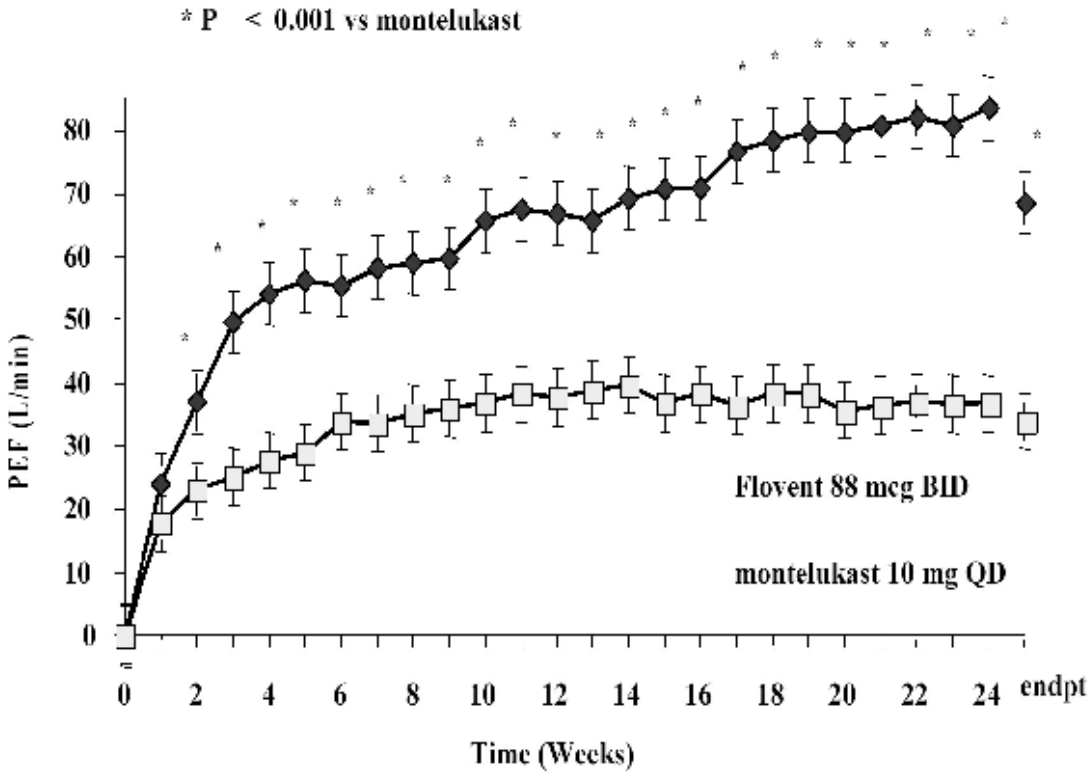
Flovent 88 mcg twice daily via metered dose inhaler (CFC-MDI) was compared to montelukast 10 mg once daily in two 24-week, randomized, double-blind, double-dummy, parallel-group studies. [88] [89] Patients ≥15 years old with mild to moderate persistent asthma who were symptomatic on short-acting $beta_2$-agonists alone, had been diagnosed with asthma for at least 6 months, had a baseline FEV_1 50%-80% predicted, and ≥15% increase in FEV_1 after inhalation of albuterol were enrolled (Table 27). In addition, patients should not have used an ICS during the previous 2 months.

Table 27. Baseline Demographics of Patients [88] [89]

	Study 1		Study 2	
	***Flovent* (n = 271)**	**Montelukast (n = 262)**	***Flovent* (n = 258)**	**Montelukast (n = 264)**
Mean age, years	35.4	34.4	36.2	35.4
Mean FEV_1 % predicted	65.6	65.4	65.6	65.9
Albuterol use, puffs/day	5.07	5.29	5.05	5.25
Mean symptom score*	1.65	1.69	1.62	1.57
Nighttime awakenings per night	0.99	0.96	0.94	0.93
* 6 - point scale				

Study 1 : *Flovent* was significantly more effective than montelukast in improving FEV_1 with a mean increase of 0.51 L (22.9%) versus 0.33 L (14.5%) over baseline ($P < 0.001$), AM PEF (mean increase of 68.5 versus 34.1 L/min over baseline, $P < 0.001$) (Figure 7), and PM PEF (mean increase of 53.9 versus 28.7 L/min over baseline, $P < 0.001$). [88]

Figure 7. AM PEF Mean Change from Baseline [88]



Additionally, patients receiving *Flovent* had significant improvements (from baseline) versus the montelukast group in:

- mean asthma symptom scores (-0.85 versus -0.60, $P < 0.001$)
- percentage of symptom-free days (32.0% versus 18.4%, $P < 0.001$)
- rescue albuterol use reduction (3.1 vs. 2.3 puffs/day ($P < 0.001$)
- rescue-free days (45.9% versus 31.2%, $P < 0.001$)
- nighttime awakenings, *Flovent* (n = 167) versus montelukast (n = 161) (-0.64 versus -0.48, $P = 0.023$) in patients with ≥ 2 awakenings per week at baseline
- withdrawals from the study due to lack of efficacy and exacerbations (15 versus 26, $P < 0.05$)

The number of patients experiencing an asthma exacerbation were not statistically different in the groups receiving *Flovent* and montelukast (12 versus 21 patients, respectively, $P = 0.106$). Physician assessment of efficacy was significantly better for patients treated with *Flovent* compared with the montelukast group ($P < 0.001$). Patient-rated overall satisfaction with their study medication was 85% of patients taking *Flovent* compared with 65% of the montelukast group ($P < 0.001$). Treatment with *Flovent* resulted in a statistically greater improvement in asthma-related quality of life compared with montelukast treatment ($P \leq 0.001$); however, a clinically meaningful change (≥ 0.5 point change) only occurred in 2 of 3 domains. The number of adverse events reported was similar between the two treatment groups. The most common ICS-related adverse events were headache (3% and 1%), sore throat (2% and 2%), hoarseness (2% and 0%), and oropharyngeal candidiasis (1% and 0%) for the groups receiving *Flovent* and montelukast, respectively.

Study 2: Mean morning FEV_1 increased 0.48 L (22%) in the group receiving *Flovent* 88 compared with 0.32 L (14%) in the montelukast group ($P \leq 0.001$). [89] AM and PM PEF improvement from baseline was significantly greater in the group treated with *Flovent* compared with the montelukast group ($P < 0.001$ for both AM and PM PEF). Additionally, the patients treated with *Flovent* displayed significantly better improvement in the percentage of symptom-free days, percentage of rescue-free days, asthma

symptom scores, reduction in rescue albuterol use, and nighttime awakenings compared with montelukast patients ($P \leq 0.01$ for all comparisons).

Physician assessment of effectiveness and overall patient satisfaction with study treatment were significantly greater in the group receiving *Flovent* compared with the montelukast group ($P \leq 0.001$). Asthma-related quality of life global score was statistically better in the patients treated with *Flovent* compared with montelukast ($P < 0.001$). The number of adverse events reported was similar for both treatment groups. The most common ICS-related adverse events were hoarseness (3% and 0%), oropharyngeal candidiasis (3% and 0%), and headache (2% and 2%) for *Flovent* and montelukast, respectively.

Flovent was compared with montelukast for 48 weeks in a 'non-inferior' (mean treatment difference of percentage of asthma-free days was below 10%) study design.[90] The study had a 3-week single-blind run-in followed by a 12-week double-blind treatment period, and a 36-week open-label period. Patients 15 to 80 years old with mild persistent asthma (Global Initiative for Asthma Guidelines) were randomized to receive *Flovent* 100 mcg (n = 320) twice daily by metered-dose inhaler or montelukast 10 mg (n = 325). The primary endpoint was asthma-free days. Secondary endpoints were $beta_2$-agonist usage, days with symptoms, rescue-free days, asthma-specific quality of life, FEV_1, morning PEF, asthma attacks, nocturnal awakenings, patient global assessment of asthma, blood eosinophil count, and tolerability.

Patients receiving *Flovent* had 6.44% (95% CI 2.24, 10.64) more asthma-free days than did patients taking montelukast. Patients in both groups showed an improvement in asthma-related efficacy endpoints, except for FEV_1 which was improved only in patients taking *Flovent*. Both montelukast and *Flovent* were well tolerated.

Flovent was compared with montelukast to determine the relative efficacy in controlling mild persistent asthma as measured by rescue-free days.[91] Patients 15 to 85 years old with mild persistent asthma (N = 400) were randomized to montelukast 10 mg once nightly or *Flovent* 88 mcg twice daily in a parallel-group study with a 12-week, double-blind period, followed by a 36-week, open-label period.

The mean percentage of rescue-free days was similar between treatments after 12 weeks (mean treatment difference of percentage of asthma-free days was below 10%): 74.9% (*Flovent*), 73.1% (montelukast); difference 1.8% (95% CI -3.2%, 6.8%). During the open-label period values were 77.3% (*Flovent*), 71.1% (montelukast); difference 6.2% (95% CI: 0.8%, 11.7%), difference of percentage of asthma-free days was not below 10%. Although both *Flovent* and montelukast significantly improved symptoms, quality of life, and symptom-free days during both treatment periods, therapy with *Flovent* resulted in greater improvements in lung function during both periods and in asthma control during open-label treatment. *Post hoc* analyses revealed a difference in rescue-free days favoring *Flovent* in patients with the poorest lung function and greatest albuterol use at baseline. In the remaining patients, the two treatments appeared to be comparable.

7.3 Comparison with Beclomethasone Dipropionate HFA in Asthma

Head - to - head comparisons as described below between *Flovent* HFA and QVAR are limited. HFA - propelled inhaler formulations and delivery systems containing the same corticosteroid may vary in performance characteristics. Therefore, attention to inhaler characteristics should be noted.

A single-blind, 6 - week period, crossover study compared *Flixotide Evohaler* (fluticasone propionate) HFA and Beclazone CFC-free (beclomethasone dipropionate, Norton Healthcare), both non - US products, in 20 patients with asthma. [92] Improvement from baseline in FEV_1 % predicted was significantly better for each group; between the groups there was no significant improvement with the 500 mcg twice daily dose versus the 250 mcg twice daily dose. The patients receiving Beclazone had a significant mean fall in urinary cortisol from baseline for both the 250 mcg and 500 mcg twice daily regimens, as well as an almost 2-fold fall for the 500 mcg twice daily regimen versus *Flixotide* 500 mcg twice daily.

Flovent CFC (chlorofluorocarbon) versus QVAR

Flovent CFC and QVAR had clinically equivalent improvements in AM PEF according to predetermined criteria, although statistically the difference was significantly better in the group receiving *Flovent* CFC (Table 28).

Table 28. *Flovent* CFC versus QVAR

Design	Patients, Treatment	Results
6-week, DB, DD, PG, equivalence trial using mean change from baseline AM PEF within ±25 L/min weeks 5-6. [93]	N = 172, symptomatic on *Flovent* 100-250 mcg or equivalent. Mean baseline FEV_1 76% to 78% predicted. Flovent CFC 400 vs. QVAR 400 mcg daily	Mean change in AM PEF: 19 (QVAR) and 30 (FP) L/min (P = 0.022). Mean change from baseline FEV_1: no significant difference. Similar improvements for asthma symptom scores, reduced rescue medication usage, % days with symptoms, and AQLQ score. Mean % change from baseline AM plasma cortisol: +17.7% (QVAR) vs. + 4.2% (FP) (P = 0.066). No statistically significant differences in adverse events.
DB = double-blind, DD = double-dummy, PG = parallel group, QVAR (beclomethasone dipropionate) HFA, 3M; AQLQ = Asthma Quality of Life Questionnaire; FP = *Flovent*		

FLOVENT HFA VERSUS QVAR: CLINICAL EFFICACY

An 8-week, open-labeled study in patients with moderate to severe asthma was conducted to determine equivalence of QVAR 800 mcg daily (n = 101) and *Flovent* HFA 1000 mcg daily (n = 97). [94] Equivalence test determination was defined as a mean change from baseline in AM PEF of within ± 25 L/min. Patients were symptomatic on 500-1000 mcg daily of beclomethasone dipropionate via CFC (chlorofluorocarbon) inhaler.

Mean FEV_1 percent predicted at baseline was approximately 72% for both treatment groups. In the intent-to-treat population, the mean change from baseline in AM PEF was 29.6 L/min in patients receiving QVAR and 17.1 L/min in patients receiving *Flovent* HFA; the difference of 12.5 L/min satisfied the definition of equivalence. No significant differences were reported for mean PM PEF, or mean change from baseline in FEV_1, forced expiratory flow of 25% of the vital capacity (FEF 25%), FEF 25-75%, or inspiratory vital capacity. In addition, similar improvements were observed for asthma symptom scores and rescue medication usage (24% vs. 19% for QVAR and *Flovent* HFA, respectively). There were no statistically significant differences in urinary cortisol/creatinine values.

FLOVENT HFA VERSUS QVAR: ADRENAL ACTIVITY STUDIES

Flovent HFA 750 mcg and QVAR 800 mcg had similar and within normal range values of 24-hour urinary cortisol excretion in asthma patients in one study. In a second study, healthy volunteers receiving QVAR 1000 and 2000 mcg daily had significantly suppressed overnight urinary cortisol compared with placebo, while only the 2000 mcg dose of *Flovent* HFA caused significant suppression versus placebo (Table 29).

Table 29. *Flovent* HFA vs. QVAR: Cortisol Measurements in Patients with Asthma and Volunteers

Design	Patients, Treatment	Results
R, 'modified blind', CO, 14-day periods, 21-day washout, % change 24 hr UCE difference within ± 20% for equivalence[95]	N = 26 adults (12 males, 16 females), stable mild-moderate asthma; *Flovent* HFA 375 mcg & QVAR 400 mcg twice daily	Both groups had a similar reduction in 24 hr UCE. • Day 1, mean UCE: 333.83 (QVAR); 320.79 (*Flovent* HFA) nmol/24hr. • Mean change (Day 1-14): -101.65 nmol/24hr (28.54%) in QVAR group; -91.53 nmol (22.80%) in *Flovent* HFA group. Plasma cortisol results remained within lower limit of normal (28-362 nmol/24hr)
R, PL-C, SB, CO, 3-week periods, 1-week run-in and washout. Measured 22:00 - 8:00 and AM UCE/Cr, AM serum cortisol[96]	N = 16 healthy volunteers, mean age 24.8 years. *Flovent* HFA or QVAR 500, 1000, 2000 mcg daily: 1 week at each dose	Cortisol measures showed a dose-related effect. QVAR: a significant suppression of overnight & AM UCE/Cr (1000, 2000 mcg) and AM serum cortisol (2000 mcg) was observed vs. PL (P <0.05). *Flovent* HFA: 2000 mcg suppressed all 3 measures vs. PL (P <0.05). Geometric UCE/Cr mean fold difference (95% CI) was: • 2.31 (1.41-3.76) *Flovent* HFA 2000 vs. PL • 2.65 (1.63-4.33) QVAR 2000 vs. PL • 1.74 (1.11-2.73) QVAR 1000 vs. PL • 1.64 (1.04-2.56) QVAR 1000 vs. *Flovent* HFA 1000 (P<0.05)
24 hr UCE = 24-hour urinary cortisol excretion, R = randomized, CO = crossover, PL-C = placebo-controlled, SB = single-blind, Cr = creatinine, QVAR (beclomethasone dipropionate) HFA, 3M		

7.4 Comparison with Mometasone Furoate in Asthma

EFFICACY OF *FLOVENT* COMPARED WITH MOMETASONE FUROATE (MF)

An open-label, multi-center, randomized, parallel-group study compared the efficacy of *Flovent* (CFC: chlorofluorocarbon propellants) Inhalation Aerosol 250 mcg twice daily to that of MF 400 mcg administered via a dry powder inhaler (MF-DPI) every evening (QPM) for 8 weeks. [97] One hundred sixty-seven adolescents and adults age 13-80 years old with moderate persistent asthma using daily treatment with *Flovent* were included in the study.

The primary efficacy endpoint was the mean change from baseline at endpoint in forced expiratory volume in 1 second (FEV_1). Secondary endpoints included morning and evening peak expiratory flow rates (PEF), forced vital capacity (FVC), asthma symptom scores, rescue albuterol use, physicians' evaluations of patient's response to therapy, and patients' device evaluations.

At baseline, the groups were comparable with respect to mean age (43 years), duration of asthma (15 years), percent predicted FEV_1 (76%), and previous dose of inhaled *Flovent* (68% - 69% at 500 mcg daily).

Although there were greater numerical improvements with *Flovent* in the primary and most secondary endpoints, the differences were not statistically significant, with exception of the physician assessment (Table 30).

Table 30. *Flovent*: Mean Change from Baseline at Endpoint

	***Flovent* MDI 250 BID (n = 85)**	**MF-DPI 400 QPM (n = 82)**
FEV_1, L	0.16	0.11
Morning PEF (L/min)	18.4	10.9
Evening PEF (L/min)	12.5	8.3
FVC (L)	0.12	0.08
Daytime asthma symptom scores (0-3 scale)	-0.2	-0.1
Nighttime asthma symptom scores (0-3 scale)	-0.1	0.1
Albuterol use per day (puffs + nebulizer use; 1 nebulizer treatment = 6 puffs)	-0.8	0.2
Physician Assessment (%) (improved + much improved)	47	62*
* $P = 0.007$; statistical comparisons based on 90% confidence interval		

Treatment related adverse events were mild to moderate in severity and were reported with similar frequency in the groups treated with *Flovent* (8.2%) and MF-DPI (13.4%). The most commonly reported event was headache (2.4% and 3.7% , respectively).

The efficacy of *Flovent Rotadisk* was compared to that of MF administered via a dry powder inhaler (MF-DPI) in a 12-week, randomized, active control, single-blind study.[98] Adolescents and adults >12 years of age (N = 733) with FEV_1 60%-90% of predicted who were previously treated with inhaled corticosteroids were included in the study. Patients were randomized to one of four treatment arms: MF-DPI 100 mcg, 200 mcg, or 400 mcg twice daily (double-blinded), and *Flovent Rotadisk* 250 mcg twice daily (single-blinded) for 12 weeks.

The primary efficacy endpoint was mean change from baseline at endpoint for FEV_1. Secondary endpoints included morning and evening PEF, FVC, forced expiratory flow 25% to 75% ($FEF_{25\%-75\%}$), asthma symptom scores, rescue albuterol use, nighttime awakenings, and physicians' evaluations of patient's response to therapy. The groups were comparable with respect to mean age (40-42 years), duration of asthma (13-16 years), $FEV_1$75%-76% predicted, and prescribed ICS use. The study was designed to detect a 0.15 L difference (6%) in mean change from baseline between any two treatment groups. The mean change from baseline at endpoint in FEV_1, FVC, and albuterol use was similar for *Flovent Rotadisk* compared with all doses of MF-DPI (Table 31). *Flovent Rotadisk* showed significant improvements in AM PEF, $FEF_{25\%-75\%}$ and nocturnal awakenings compared with MF-DPI 100.

Table 31. *Flovent*: Mean Change from Baseline at Endpoint

	***Flovent Rotadisk* 250 BID, n = 184**	**MF-DPI 100 BID, n = 182**	**MF-DPI 200 BID, n = 182**	**MF-DPI 400 BID, n = 184**
FEV_1 (L)	0.16	0.07	0.16	0.19*
Morning PEF (L/min)	32*	15	29*	30*
$FEF_{25\%-75\%}$ (L/sec)	0.25*	0.04	0.21	0.28*
FVC (L)	0.08	0.03	0.08	0.11
*$P \leq 0.05$ compared with MF-DPI 100				

	***Flovent Rotadisk* 250 BID, n = 184**	**MF-DPI 100 BID, n = 182**	**MF-DPI 200 BID, n = 182**	**MF-DPI 400 BID, n = 184**
Nocturnal awakenings	-0.14*	0.07	0.01	-0.06
Albuterol use (mcg/day)	-52.06	-13.23	-94.84*	-38.10
*$P \leq 0.05$ compared with MF-DPI 100				

Asthma symptom scores including morning wheeze, difficulty breathing, and cough, improved to a similar extent in all treatment groups. The only significant difference was observed in favor of *Flovent Rotadisk* vs. MF-DPI 100 and 200 for morning difficulty breathing ($P \leq 0.05$). The number of physicians who rated their patients' asthma as "much improved" was similar for *Flovent Rotadisk*, MF-DPI 200 and 400 (60-62%) which were significantly greater than MF-DPI 100 (53%, $P \leq 0.05$).

Both *Flovent Rotadisk* and MF-DPI were well tolerated, and there were no unexpected adverse events reported. Treatment-related pharyngitis (12-16%) and dysphonia (2-7%) were comparable among groups. Percent of patients experiencing oral candidiasis was 1% (MF-DPI 100), 7% (MF-DPI 200), and 10% (MF-DPI 400 and *Flovent Rotadisk*). One patient who received *Flovent Rotadisk* discontinued therapy because of oral candidiasis. Overall, 32 patients discontinued the study because of an adverse event, which were distributed similarly among groups (3-5%) and included worsening asthma, bronchitis, pharyngitis, and upper respiratory tract infection.

Effect on HPA-Axis

A 2-week, randomized, 2-way cross-over study compared MF (via Twisthaler) 400 mcg twice daily (MF-DPI) and *Flovent Diskus* 400 mcg twice daily on 24-hour serum cortisol in 27 patients with mild to moderate asthma.[26] Previous inhaled corticosteroid therapy was discontinued for 5 days before baseline assessments. MF-DPI and *Flovent Diskus* were administered sequentially without a wash-out period. The percent change from baseline in the 24-hour serum cortisol was 2-fold greater for MF-DPI compared with *Flovent Diskus*; 35% and 18%, respectively.

A study assessed overnight urinary cortisol/creatinine as the primary outcome of adrenal suppression in 21 patients with persistent asthma (mean FEV_1 91% predicted). [99] Patients were randomized in a crossover fashion to receive 2 weekly consecutive doubling incremental doses of either *Flovent Diskus* 500, 1,000, and 2,000 mcg/day or MF 400, 800, and 1,600 mcg/day (via Twisthaler) (MF-DPI). For the 21 per protocol completed patients, there was significant suppression compared with baseline in overnight urinary cortisol/creatinine for the high and medium doses of both drugs (Table 32). Cross-treatment comparisons were not assessed. For the secondary outcomes of 8:00 AM plasma cortisol, serum osteocalcin, and early morning urinary cortisol/creatinine, there was significant suppression compared to baseline for the highest dose of each drug.

Table 32. Percent Change From Baseline in 10-hour Urinary Cortisol/Creatinine

Treatment	Mean % Decrease	95% Confidence Interval	P - Value vs. Baseline
Flovent Diskus 500	5.66%	-25.00, 12.28	1.00
Flovent Diskus 1000	31.03%	6.54, 48.98	0.02
Flovent Diskus 2000	45.95%	17.36, 64.54	0.002
MF-DPI 400	14.53%	-13.64, 35.48	0.54
MF-DPI 800	28.06%	3.85, 46.81	0.02
MF-DPI 1600	47.92%	20.63, 65.87	0.001

A multi-dose, randomized, evaluator-blinded, placebo-controlled, parallel study was conducted to compare the effects of MF and *Flovent* on 24-hour serum cortisol levels and adrenal response to

cosyntropin stimulation testing. [43] Sixty-four adult patients with moderate persistent asthma who were not previously receiving inhaled corticosteroids were randomized to treatment with MF 400 or 800 mcg (HFA formulation) (MF-MDI) twice daily, *Flovent* CFC 880 mcg twice daily, or placebo for 29 days. All treatments were administered via metered dose inhalers. HPA axis function was measured at baseline and weekly for four weeks for serum cortisol levels and area under the curve for serum cortisol over a 24-hour period ($AUC_{24\ hr}$). Cosyntropin stimulation testing with 0.25 mg cosyntropin was performed on day 29. At baseline, all patients had similar mean serum cortisol $AUC_{24\ hr}$.

Mean serum cortisol $AUC_{24\ hr}$ for MF-MDI 400 mcg was not significantly different than placebo. However, MF-MDI 800 mcg significantly reduced $AUC_{24\ hr}$ compared with placebo by 20%, 30%, and 22% on days 14, 21, and 28, respectively. Serum cortisol $AUC_{24\ hr}$ was also suppressed for *Flovent* 880 mcg by 43% to 56% which was significant compared with MF-MDI 800 mcg. Despite these reductions, all patients demonstrated a normal response to cosyntropin stimulation testing on day 29.

8. OTHER STUDIED USES

8.1 Use of *Flovent HFA* in Children Less than 4 Years of Age with Asthma

FLOVENT HFA: CLINICAL INFORMATION

In a 12-week, randomized, double-blind clinical study, the efficacy and safety of *Flovent* HFA was compared with placebo in children 12-47 months old with asthma.[100] Patients were required to have at least two episodes of increased asthma symptoms requiring medical attention and pharmacotherapy within the previous 12 months. After a 2-4 week run-in period, patients were randomized if they had a 24-hour symptom score of ≥ 1.1 and had used rescue albuterol ≥ 3 times per week for 2 consecutive weeks (Table 33). Children (N =359) were randomized 2:1 to receive either *Flovent* HFA 88 mcg (2 inhalations of 44 mcg) twice daily or placebo both via AeroChamber Plus® with attached face mask. The primary endpoint was mean percent change from baseline to endpoint in 24-hour daily asthma symptom score.

Table 33. Patient Characteristics: Baseline Mean Scores[100]

Mean Scores	Flovent HFA	Placebo
Duration of asthma (months)	21.9	21.8
24-hour asthma symptom scores	1.8	1.7
Daytime asthma symptom scores	1.6	1.5
Nighttime asthma symptom scores	1.4	1.2
Rescue albuterol use (puffs/day)	4	5
Symptom scoring: 0 = no symptoms to 3 = severe symptoms		

Patients treated with *Flovent* HFA had greater improvement in asthma symptoms scores compared with the placebo group (Table 34).

Table 34. Primary and Secondary Endpoints - Mean Change from Baseline at Endpoint[100]

Efficacy	Flovent HFA	Placebo	P-value
Reduction in 24-hour asthma symptoms scores	54%	44%	0.036
Nighttime symptom scores	-0.68	-0.54	0.048
Daytime symptom scores	-0.81	-0.66	0.048
Daily rescue albuterol use (puffs/day)	-3	-2	--
Patient withdrawal due to treatment failure	5%	12%	0.034
Treatment failure defined as clinical exacerbation requiring protocol-prohibited asthma medication and/or hospitalization			

Seven patients treated with *Flovent* HFA and two patients treated with placebo withdrew due to adverse events. The majority of these withdrawals were due to infection and not considered drug-related. The incidence of investigator-determined drug-related adverse events was 4% in each treatment group. Exacerbations occurred in 11% of patients treated with placebo and 4% of patients treated with *Flovent* HFA. The change in 12-hour urinary cortisol levels was similar between groups with no clinically significant change from baseline.

A 12-week, randomized, double-blind, parallel-group study evaluated the safety and efficacy of *Flovent* HFA in 160 children 12 to 47 months old with persistent asthma symptoms including cough, wheeze and shortness of breath.[101] The patients received either *Flovent* HFA 44 mcg two puffs twice daily (n =79) or placebo (n =81) with the Babyhaler™ spacer device. The primary endpoint was the percent of symptom-free 24-hour days.

The results were clinically as well as statistically significantly different. Patients receiving *Flovent* HFA had more symptom-free 24-hour days compared with the placebo group (OR 0.53, 95% CI 0.29, 0.95; P = 0.035) which equaled one more symptom-free 24-hour day per week. Patients receiving *Flovent* HFA also had more cough-free 24-hour days per week (OR 0.54, 95% CI 0.30, 0.96; P = 0.038) and more wheeze-free 24-hour days per week (OR 0.28, CI 0.15, 0.53; $P < 0.001$) compared with the placebo group. The overall treatment-related adverse events were similar between groups. The morning urinary-free cortisol adjusted geometric mean ratio *(Flovent* HFA/placebo) was 0.79 (P = 0.044). There were no adverse events related to low cortisol levels.

Long-Term Safety and Efficacy

A 52-week, non-US, randomized, open-label study evaluated the long-term safety and efficacy of *Flovent* HFA in children 12 to 47 months old with recurrent or persistent cough, wheeze or asthma-like symptoms. [56] More than 50% of patients had been hospitalized for these symptoms in the previous year, and more than 30% had been on regular inhaled corticosteroids. Patients (N = 625) were randomized 3:1 to receive either *Flovent* HFA 88 mcg twice daily with Babyhaler spacer or sodium cromoglycate (SCG) 5 mg daily with Nebuhaler spacer for 52 weeks.

Mean adjusted growth rate (n = 443) was not affected by *Flovent* HFA: the growth rate was 84 mm/year for the group receiving *Flovent* HFA and 86.4 mm/year for the SCG group. Mean serum cortisol concentrations showed a statistically significant suppression of 10% [240.8 (*Flovent*) versus 267.9 nmol/L (SCG); P = 0.050]. At baseline, 11 children in the *Flovent* HFA group had serum cortisol levels below the lower limit (83 nmol/L); only 3 children had this level at study end. Similarly, in the SCG group, 4 and 0 children had this level at baseline and end of study, respectively. Twelve-hour urinary-free cortisol/creatinine corrected was reduced by 14% after *Flovent* HFA treatment (28.2 vs. 33.0 nmol/mmol for SCG; P = 0.008). Urinary cortisol concentrations decreased by ≥50% in 13% and 11% of the *Flovent* HFA and SCG groups, respectively. The most common treatment-related events were cough (*Flovent* 2%

vs. SCG 1%) and hoarseness (*Flovent* 1% vs. SCG 0%). One patient had a cataract identified by slit-lamp examination following treatment with *Flovent* HFA; this resolved after 12 months.

The efficacy of *Flovent* HFA was significantly better compared with results in the SCG group. Patients receiving *Flovent* HFA had greater improvement in symptom-free days (OR 0.49, 95% CI 0.33, 0.72 $P < 0.001$), days without rescue medication (OR 0.56, 95% CI 0.34, 0.93 $P = 0.023$), and fewer patients experienced asthma exacerbations (34% vs. 47%, $P = 0.002$).

9. OUTCOME AND ECONOMIC EVALUATION

To date, there are no pharmacoeconomic evaluations of *Flovent HFA*. *Flovent* Inhalation Aerosol and *Flovent Rotadisk* are no longer being manufactured and marketed in the U.S. Pharmacoeconomic analyses on all formulations of *Flovent* are included in the following tables.

Patients receiving FP had lower asthma care costs and significantly lower risks of asthma-related hospitalizations in several pharmacoeconomic studies compared with patients treated with montelukastTable 35.

Table 35. *Flovent* (FP): Comparisons versus Montelukast (MON) in Patients with Asthma

Study	Dose	Results
(102)Stempel DA, et al. Retrospective health care payer economic evaluation of patients started on FP or MON in 8 MCOs over 9 months. Adjusted mean costs analyzed for all asthma treatment medications & resources (hospital, ED visits, physician office visits).	FP 44 mcg (n=318) vs. MON 5, 10 mg (n=575)	FP group vs. MON group had: significantly lower asthma care costs regardless of severity significant reductions in emergency department & hospitalization costs
(103) Retrospective database claims analysis N=505 (FP) & 1875(MON) patients enrolled in MCO 1 year with no pharmacy claims for other ICS or LTM prior to initial FP or MON claim, & ≥2 claims for either drug with no switching of controller medication. Baseline prednisone and ALB usage similar.	FP 44 mcg or MON as initial monotherapy controller medication	FP group vs. MON group had: lower hospitalization rates (1.4% vs. 3.4%, P=0.017) lower status asthmaticus rates (2.4% vs. 4.4%, P=0.041) longer time to either event (P≤0.006). received lower doses of prednisone & ALB (P<0.001)
ZA=zafirlukast, LTM=leukotriene modifier, ALB=albuterol		

[104]Pathak et al. 9-month, observational study using pharmacy & medical claims to compare asthma care cost in patients newly started on MON, ZA or low-dose FP, with no claim for any ICS or LTM in prior 9 months. N=284 patients with asthma. Adjusted for age, gender, etc.	FP 44, 110 mcg (n=284) or MON 5 or 10 mg (n=302) or ZA 10 mg (n=195)	FP 44, 110 mcg vs. MON & ZA groups had significantly lower asthma claims costs per patient: $528, $967, & $1359, respectively. ZA & MON groups had 3.4 & 1.9-fold, respectively, increased risk of an asthma-related hospitalization and were 7.2 & 4.9 times, respectively, more likely to switch or add another controller
[105]Stanford et al. 12-month cost-effectiveness comparing asthma-related hospitalizations & health care costs. N=1177 patients with asthma, >4 years old initially prescribed FP or MON (1997-2000). Asthma related costs & risk of asthma-related hospitalization were adjusted for age, gender, heath plan, metropolitan area, co-morbidities, pre-asthma related costs, asthma severity.	FP 44 mcg (n=400) or MON 10 mg (n=777).	FP patients vs MON patients had: 49% lower asthma care costs (95% CI 38%, 61%) 16% lower total healthcare costs (95% CI 7.6%, 23%) lower risk of an asthma related hospitalization (OR 0.12, *P*=0.043) switched or added therapy significantly less had significantly lower asthma care costs in age group analysis of 4-17 & ≥18 years old
ZA=zafirlukast, LTM=leukotriene modifier, ALB=albuterol		

Two cost-consequence analyses have compared asthma-related costs associated with FP and montelukast therapy. [106,107] In one of these studies, FP use, but not montelukast use, significantly reduced asthma-related costs. Significant reductions in both emergency department and hospitalization costs were associated with FP initiation. Similar changes in asthma related costs associated with FP or montelukast use were found in the second study. However, the absence of a difference between FP and montelukast may be due to the relatively small numbers of patients evaluated (209 for FP and 94 for montelukast) or the differences in prescription refills (5.8/year for montelukast and 3.2/year for FP). In another cost-consequence analysis, use of FP was associated with a significant reduction in the mean total healthcare costs as compared to use of montelukast, zafirlukast, or zileutin [108]

Results from a retrospective cohort analysis using pharmacy and medical claims supports *Flovent* as being associated with significantly lower asthma care as well as lower total healthcare costs compared with other inhaled corticosteroidsTable 36.

Table 36. *Flovent* (FP): Cost-Analysis Compared with other Inhaled Corticosteroids

Study	Dose	Results
[109]1-year retrospective cohort analysis of pharmacy & medical claims (Pharmetrics Integrated Outcomes®) to determine differences in asthma care costs. N=1956 patients with ICD-9 (493.XX) claim for asthma & newly prescribed an ICS	FP 44mcg, BDP, BUD, TAA, FLU	Annual asthma care charges (pharmacy & medical) were significantly higher (P<0.03) in patients treated with BDP, TAA, BUD & FLU vs. FP (24%, 27%, 34%, & 45%, respectively. Asthma and non-asthma charges were significantly higher ($P \leq$0.005) in patients treated with BDP, TAA, & FLU vs. FP (53%, 46%, and 39%, respectively)
*Daily dosage information not available from the database, BDP=beclomethasone dipropionate, BUD=budesonide, TAA=triamcinolone acetonide, FLU=flunisolide, ICS=inhaled corticosteroid		

Flovent was more cost-effective and more efficacious in most trials compared with budesonide in adults and pediatrics with asthma Table 37.

Table 37. *Flovent* (FP): Comparison with Budesonide (BUD) in Patients with Asthma

Study	Dose	Results
[110] Retrospective, CE using data from [111]meta-analysis (6 open-label, 1 DB European trials) ≈ 2,000 adults & children with mild to severe asthma. Costs: study med, other meds, asthma-related adverse events, hospitalizations, physician 24-hour callout, & emergency room. Efficacy success defined as an increase in daily AM PEF of 10% or >15 L/min.	Mcg of FP ≤1/2 mcg BUD powder	Mean total daily cost/patient: $2.25 (FP) vs. $3.00 (BUD). AM PEF: FP (40%) had greater efficacy (P<0.0001) vs. BUD (30%), SFD: FP (44%) vs. BUD (40%, P<0.05), and EFD: FP (32%) vs. BUD (27%, P<0.05). Mean cost per STP per day: $5.62 (FP) vs. $10.05 (BUD); SFD: $4.36 (FP) vs. $6.67 (BUD), EFD: $5.60 (FP) vs. $9.42 (BUD).
[112]Retrospective CE (2 open-label, R, 6-week trials), N=457 steroid-naïve asthmatics. Costs: study & rescue meds, adverse events, office visits, & hospitalization. STP & mean % of SFD.	FP 500 mcg/day vs. BUD 1200 mcg/day.	Mean daily cost per patient: FP (DM† 4,23); BUD (DM 5,19). CE ratios: STP: FP (DM 9,00); BUD (DM 12,36). SFD: FP (DM 10,58); BUD (DM 15,26). Univariate sensitivity analysis supported the results.
SFD=Symptom-free day, STW or STD=successfully treated week or day, EFD=episode-free day, CE=cost-effectiveness, † DM=Deutschmarks, R=randomized, PG=parallel group, DB=double-blind, STP=successfully treated patient		

A cost- minimization analysis showed similar costs for the FP and budesonide groups Table 38.

Table 38. Flovent (FP): Cost-Minimization Comparison with Budesonide (BUD)

Study	Dose	Results
[113]Cost-minimization analysis of a 8-week, R, PG, open-label trial. N=221 patients with mild asthma, 18-70 years old. Primary efficacy: PEF (STD= ↑ of 5% of predicted PEF). Costs: study & rescue med, drug-related adverse events. Healthcare resources not included.	FP 200 mcg BID, BUD 400 mcg once daily, or BUD 200 mcg BID	No significant differences in SFD, % predicted PEF, or med costs only were observed among the groups.
STD =Successfully-treated day, R=randomized, PG=parallel group, DB=double-blind, BID=twice daily, SFD=symptom-free day		

Daily cost for a successfully-treated patient with asthma was lower for the FP group versus the cost for the triamcinolone-treated adults Table 39.

Table 39. Flovent (FP): Cost-Effectiveness (CE) vs. Triamcinolone Acetonide (TAA)

Study	Dose	Results
[114]CE of R, open-label US study in asthma clinics. N=304 adults, >17 years old, previously untreated for asthma. Costs of asthma-related events, medications, SFD compared.	TAA vs. FP Physicians determined the initial dose & modified treatment as needed	Mean asthma-related costs were $1141 (FP) vs. $1080 (TAA). The FP patients had more SFD vs. the TAA group (156.7 vs. 130, respectively). The incremental CE ratio was $2.35 per SFD for FP (95% CI -$4, -$28).
[115]CE of 2 parallel group, 24-week, R, DB, PL-C U.S. studies. N=397 patients with moderate asthma. Total cost: study & rescue meds, drug-related adverse event, emergency room visits, unscheduled physician visits, work/school days missed.	FP powder 250 mcg (Diskhaler) BID or TAA 200 mcg CFC MDI QID	Mean daily direct cost per patient: $2.24 (FP) & $2.19 (TAA). Total direct & indirect costs: $2.53 (FP) & $2.74 (TAA). FP group had a significantly higher % of STP (47% vs. 26%, P<0.001) vs. TAA group. Daily cost per STP was lower for the FP subjects for direct ($4.78 vs. $8.32) and direct + indirect costs ($5.38 vs. $10.44) vs. TAA-treated patients.
QID=four times daily, CFC=chlorofluorocarbon propellant, TAA=triamcinolone acetonide, , SFD =symptom-free days, PL-C=placebo-controlled, R=randomized, STP=successfully treated patients had 15% increase in FEV1 from baseline		

The difference in cost-effectiveness ratios for the FP group compared with the flunisolide group indicated more symptom-free days and greater increases in lung function balanced with medication costs Table 40.

Table 40. *Flovent* (FP): Cost-Effectiveness (CE) Versus Flunisolide (FLN) in Adults with Asthma

Study	Dose	Results
[116]Retrospective CE of prospective 6-week, open-label (n=332) & 8-week DB (n=308) studies. Patients with moderate asthma, no steroids prior 3 weeks, 18-70 years old. Direct costs were adjusted to 1997 DM.	FP 250 mcg BID CFC MDI, FLN 500 mcg CFC MDI BID	The FP group had greater increases in AM & PM PEF (P<0.01), successfully treated patients, & % symptom-free days vs. FLN group. Both drugs were well tolerated. FP group had 22% (open-label) & 16% (DB study) greater increase in symptom-free days from baseline vs. FLN. All CE ratios were lower for FP vs. FLN groups. Sensitivity analysis showed robust results (±10%).
STD =Successfully-treated day, R=randomized, PG=parallel group, DB=double-blind, BID=twice daily, SFD=symptom-free day		

Severe steroid dependent asthmatics treated with FP 1760 mcg/day had significantly less asthma-related healthcare utilization over 1 year than in the previous year while not receiving FPTable 41. Also, patients had a significant reduction in work days lost due to asthma.

Table 41. Flovent (FP): Healthcare Utilization When Added to Prednisone Therapy

Study	Dose	Results
[117]Retrospective comparison to health utilization and costs of previous 12-month, open-label study in 24 steroid-resistant patients with severe asthma. Costs: study drug, oral prednisone, emergency room, unscheduled asthma-related visit or hospitalization, ICU stay, & specialty center. Indirect costs: lost wages, benefits. Improvement (P<0.05) in the # asthma-related visits, steroid bursts, # days hospitalized, missed from work or school.	FP 1760 mcg daily added to oral prednisone attempting to decrease prednisone dose.	Monthly direct cost per patient: $1017 after FP; $1402 before FP. Monthly indirect plus direct costs per patient: $1028 after FP; $1827 before FP.

FP 100 mcg daily was more cost-effective than sodium cromoglycate in improving PEF and symptom control in children 4-12 years old with asthmaTable 42. In another study, FP 100 mcg twice daily rated a better cost-effectiveness ratio compared with placebo in children 12-47 months old with asthma.

Table 42. Flovent (FP): Cost-Effectiveness (CE) in Children

Study	Dose	Results
[118]Cost effectiveness of a 8-week study in 225 children 4-12 years old with asthma who required inhaled prophylactic therapy.	FP powder 50 mcg BID (Diskhaler), sodium cromoglycate (SC) powder 20 mg QID	For each £ spend, FP was associated with twice as many successfully treated patients vs. SC based on the British Thoracic Society's asthma guidelines.
[119]Cost-effectiveness (Danish, 1999 values) of R, DB, PL-C, 12-week trial. N=237 children 12-47 months old with asthma symptoms. Efficacy: # patients free of exacerbations, SFD, % patients 25% improvement in cough-free & wheeze-free days. Costs of asthma-related events, adverse events & medications.	FP 50 mcg, 100 mcg or Placebo BID Both MDI plus Babyhaler spacer device	FP 100 group (74%) were exacerbation-free vs. 59.8% in Placebo group. Patients in FP 100 group (58%) vs. Placebo (39%) had a decrease in coughs. Total direct health-care costs per patient per day were lower in FP 50 & 100 vs. Placebo group: $1.73, $1.80, and $2.60, respectively. The incremental CE ratios indicated that FP 200 mcg/d achieved endpoints at a lower overall cost vs. Placebo
[120]Cost-effectiveness of R, open-label, PG, 4-week study in UK‡ hospitals & general practices. Children 4-11 years old. Efficacy: ≥5% increase AM PEF. Sensitivity tested for 1% & 10% PEF increase.	FP 100 mcg BID (n=139) or BUD 200 mcg BID (n=137).	STP: 47.5% (FP) vs. 26.3% (BUD). Total mean cost/patient/4 weeks: FP (£13.64) vs. BUD (£12.36). Cost per STP: FP (£28.72) vs. BUD (£47.00).
BID=twice daily, QID=four times daily, Costs reported in £UK, SFD=symptom-free days, MDI=metered dose inhaler, R=randomized, DB=double-blind, PL-C=placebo-controlled, STP=successful-treated patient		

Enclosure: Prescribing Information for *Flovent Diskus*

Enclosure: Prescribing Information for *Flovent HFA*

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